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THE ACUTE COR PULMONALE *

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THE limits of the field of simple clinical observation have not yet been reached. There are still puzzles to solve and new observations to make at the bedside itself or in the office and without the need of elaborate apparatus or extensive knowledge of chemistry or physics. I shall relate to you today an interesting experience of my own and its development by Dr. Sylvester McGinn and myself, in the field of clinical observation, which has resulted in an advance of our knowledge in internal medicine. The new ground which we have occupied is still in a rough condition and needs to be further explored and consolidated. We have searched the literature but have found only statements indicating that this is a direction in which an advance is needed and the mention of some of the signs that we have grouped together. I shall come back to these statements later on.

Case 1. On October 20, 1932, two and one-half years ago, I was asked to see a professor, 42 years old, who was suffering from an acute complication during his convalescence from a surgical operation, which had consisted of the removal of a gangrenous appendix with the establishment of drainage. The day before my examination, which was 30 days after the operation, he was suddenly seized with substernal distress and dyspnea, his pulse rate rose to 130, and his blood pressure fell to 90 millimeters systolic and 70 diastolic. When I examined him I found his skin slightly pale and cyanotic, his heart apparently normal in size but with poor sounds at the apex, marked accentuation of the pulmonary second sound, visible and palpable systolic pulsation in the second left intercostal space near the sternum over the pulmonary artery, and a slight to and fro friction rub just at the left of the sternum in the third and second intercostal spaces. The pulse rate was 100, the blood pressure 120 systolic and 90 diastolic, and the temperature was 100.8°; the respiratory rate was 35 to 40; and the leukocyte count had risen from 12,800 of the day before to 28,000. His electrocardiogram taken two hours after the attack of October 19 showed sino-auricular tachycardia with prominent S-waves and slightly low origin of the T-waves in Lead I, low T-waves with gradual ascent in Lead II, and deep Q-waves and late inversion of the T-waves in Lead III. A tentative diagnosis of acute coronary thrombosis was made. The next day he was still very ill, there was now an increased venous pulse in the neck, the friction rub was diminished, and signs of pulmonary infarction on physical examination (dullness and bronchial breathing) and by roentgen-ray had developed at the angle of the right scapula. The diagnosis was

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changed to extensive pulmonary embolism with acute dilatation of the right heart (the acute cor pulmonale). Helpful in establishing this diagnosis were two other episodes during convalescence from the operation, both of which were obviously pulmonary infarcts of moderate but not high degree, one on the ninth and the other on the forty-ninth postoperative day; four days after the first pulmonary infarct a phlebitis of the right lower leg became evident. There was no further trouble and the patient was discharged to his home 94 days after the operation in good health and with a normal electrocardiogram. He has remained well since.

Three other cases illustrating various features of this subject are worthy of brief note before we consider in detail the signs of the acute cor pulmonale.

Case 2. A merchant, 48 years old, consulted me on August 29, 1933, because of two attacks which had suggested to his family doctor some trouble with his heart. Four weeks before, he had been seized by epigastric pain extending up into the left chest but not preventing him from driving his car 200 miles. He spent one day in bed and then resumed work although the left chest pain persisted in decreasing degree for a week, aggravated by deep breathing. Twelve days after the first attack and while preparing breakfast he was seized by a clutching sensation or catch in the throat with difficulty in breathing. His doctor gave him morphine and put him to bed for five days. Ten days after getting up and about he came to see me, feeling very well. Examination showed nothing amiss, except that his tongue was slightly coated, his pulse rate was 96, fluoroscopy showed the heart slightly enlarged transversely with undue prominence of the pulmonary artery, and somewhat cloudy lung fields, and the electrocardiogram showed low T-waves in all leads. Recent past history revealed one very significant fact—a severe sprain of his leg on playing tennis four weeks before his first attack of chest pain; he had been laid up with swelling of the leg for about a week. Eight days after my examination the patient had a sudden collapse with dyspnea of unknown nature and died in the course of a few hours. Postmortem examination showed moderate dilatation and hypertrophy of the right ventricle with heart weight of 400 grams with no evidence of valvular, coronary, or pericardial disease but with multiple infarcts, in the lungs, a small one in the right upper lobe, another small one in the left upper lobe, a large one in the left lower lobe with laminated clot partly occluding the main left pulmonary artery and with a fresh clot superimposed upon it.

Case 3. On June 4 of last year, 1934, I was asked to see a lawyer who had been taken seriously ill the night before with an attack of substernal oppression radiating partway out to the right axilla, lasting for hours, attended by exhaustion, dyspnea, and sweating and only partly relieved through the night by repeated doses of morphine. At 4 a.m. he grew desperately ill with marked cyanosis and dyspnea. The doctor in attendance found then a to and fro friction rub at the left of the upper sternum and a diastolic gallop rhythm in the midprecordial region. He administered oxygen and carbon dioxide with great benefit. When I examined the patient at 11 a.m. he was already much improved but he showed still some dyspnea and cyanosis and his jugular veins were moderately distended and pulsating. The pulmonary second sound was accentuated and doubled but the gallop rhythm and precordial friction rub had gone. Dullness and pleural friction rub were present in the right axilla. The patient rapidly recovered and in a few weeks was in good health and back at work. Recent past history revealed a milder but otherwise similar episode with chest pain on the left one week before his severe attack and a phlebitis of his right calf after a strain while working in his garden a week before that.

Case 4. Early in January of this year a man, 41 years old, entered the surgical service at the Massachusetts General Hospital because of upper abdominal pain.

Examination showed normal heart and blood pressure. A diagnosis of gall stones was made and the gall-bladder containing several small stones was removed. On the twenty-fifth postoperative day there was sudden epigastric and lower substernal distress with great dyspnea. A state of shock followed, with ashy cyanosis, cold sweat, rapid, thready pulse and a drop in blood pressure to 75 mm. systolic and 60 diastolic. After a few hours the shock lessened and examination showed a to and fro friction rub at the left of the upper sternum and a loud diastolic gallop rhythm at the lower end of the sternum. The diagnosis rested between acute coronary occlusion and the acute cor pulmonale due to extensive pulmonary embolism. The next day both friction rub and gallop rhythm had disappeared and the patient complained of pain in the right chest and coughed up blood-tinged sputum. Roentgen-ray showed a triangular area of dullness in the right lung that was evidently a pulmonary infarct. An electrocardiogram taken 10 hours after the attack showed prominent S-waves in Lead I, low T-waves in Lead II, prominent Q-waves and inverted T-waves in Lead III, and upright T-waves in Lead IV (the precordial lead). Twenty-five days after the attack and four days before discharge from the hospital in good condition the electrocardiogram showed a considerable change with no S-waves in Lead I, normal T-waves in Lead II, no Q-waves and flat T-waves in Lead III, and flat T-waves with deeper Q-waves in Lead IV.

These four cases illustrate well the various features of what I would call the *acute cor pulmonale*, that is, dilatation of the pulmonary artery and right heart chambers with or without failure, which results from a sudden great obstruction to the pulmonary circulation, best exemplified by massive pulmonary embolism. There have been 10 other cases which have come to our observation in the past two years which have shown some of the features noted in the four cases I have cited above. In all of these 14 cases the diagnosis of pulmonary embolism was confirmed either by autopsy, in five of the six fatal cases, or by adequate clinical evidence, including roentgen-ray examination. Only rarely, however, are all the signs and symptoms that may be said to mark the acute cor pulmonale present in the same case at the time of observation. To encounter a case with just the right amount of pulmonary arterial obstruction at just the right time is rather a fortuitous occasion and yet doubtless not very rare in the work of any physician in active medical or surgical practice. It has not been difficult for us to come across these 14 cases of ours in the short period of two and one-half years.

If the pulmonary arterial obstruction is too overwhelming and complete, either death may ensue quickly or a serious state of shock which depletes the circulation and prevents the overburdening of the right heart. In such cases the signs of the acute cor pulmonale are missing until after the state of shock has subsided. If, on the other hand, the embolus is small or of only moderate size, blocking only one large or small pulmonary arterial branch or several small branches, the obstruction may be too slight to dilate the right ventricle. Experiments on animals have shown that the right heart can stand the strain of the blocking of either one of the two pulmonary arteries without dilating, that is, without the occurrence of the acute cor pulmonale. Finally, the existence of the maximum stage of the acute strain on the right heart may be brief, a matter of hours sometimes, rather than

days, and then the physician may make his examination only after the acute cor pulmonale has in large part or wholly subsided. With these points in mind let us now turn to the diagnosis of this condition.

Diagnosis of the Acute Cor Pulmonale

1. *The Recent Circumstances.* Of great help in the diagnosis of pulmonary embolism, which is the cause of the acute cor pulmonale, is the knowledge of the recent history of the patient. A surgical operation, especially one involving abdomen or pelvis, an accident causing fracture or strain, especially of the legs, and a past or recent phlebitis even in the absence of operation or accident are very significant in differential diagnosis. Infrequently, if the patient has heart disease the source of the embolus may be the right auricle itself. The acute cor pulmonale is more commonly found in middle aged and old persons than in youth.

2. *Onset.* The onset is abrupt and in that respect resembles acute coronary occlusion and dissecting aortic aneurysm from which it must be differentiated. Dyspnea is more common as the first symptom than is thoracic oppression but substernal oppression alone or accompanying dyspnea is not a rare complaint and may be misleading. Vasomotor shock with ashy pallor, thready pulse, low blood pressure, and cold sweat, is common at the onset, as it is in numerous other serious conditions. Pain in the side of the chest from pleurisy is not the earliest symptom and sometimes is delayed for many hours.

3. *Early Signs.* Frequently examination of the lungs shows no definite abnormalities in the first 12 to 24 hours or even longer after pulmonary embolism, and the roentgen-ray too may help but little at first although a high position of the diaphragm is suggestive.

When, however, the embolism is massive enough to cause a dilatation of the right heart—the acute cor pulmonale—certain early signs of such a phenomenon may appear. These are as follows:

(a) *Increased prominence and pulsation, noted by inspection and palpation, in the region of the second and third intercostal spaces just to the left of the sternum* and overlying the dilated and sometimes overactive pulmonary artery and conus (infundibulum) of the right ventricle. There may be also a loud systolic murmur and a much accentuated pulmonary second sound if the circulation is not too much obstructed. We have not heard a diastolic murmur.

(b) *Friction rub* in this same region, that is, in the second and third intercostal spaces just to the left of the sternum, to and fro in time in some cases, in others apparently with systole alone. It is this sign which has most often caused an erroneous diagnosis of coronary thrombosis. The explanation of this friction rub is not certain, but is doubtless to be sought in marked engorgement of the pulmonary artery and right ventricular infundibulum strongly impinging on the anterior thoracic wall. A somewhat

similar friction rub has been noted in a few cases of thyrotoxicosis with marked increase in the pulmonary circulation and dilated pulmonary arteries.

(c) *Gallop rhythm*, diastolic in time, heard along the left sternal border, and presumably due to dilatation of the right ventricle, much as the common protodiastolic gallop rhythm at the apex attends left ventricular dilatation and failure.

(d) *Dilatation and increased pulsation of the jugular veins.* If the pulmonary obstruction and strain on the right ventricle are of sufficient degree to cause a damming back of blood behind the right auricle the jugular veins become engorged, and pulsation may be evident in them even with the head and neck elevated at a high angle. Such a sign should not be confused with heart failure following coronary thrombosis, which incidentally is first manifested by pulmonary congestion and edema and rarely results in failure of the whole heart sufficiently early to give rise to engorgement of the jugular veins such as can easily take place from pulmonary embolism in the first few hours after the onset of trouble. We have rarely encountered enlargement of the liver in the cases of the acute cor pulmonale, perhaps because there is hardly enough time—a matter of hours—for its development.

(e) *Cyanosis.* The cyanosis which is commonly seen in cases of pulmonary embolism in contrast to cases of coronary thrombosis, is doubtless accentuated when the right heart fails and obstruction to blood flow involves the great veins.

4. *Course.* The cardiovascular signs of the acute cor pulmonale may subside quickly, in the course of hours, or last for days until death or recovery takes place. Eight of the 14 patients that we have observed have recovered.

Twelve hours or more after the onset of the pulmonary embolism fever and leukocytosis are found and their presence may further confuse the picture with that of coronary thrombosis. But usually by the time these developments have taken place lung symptoms and signs begin to appear: cough with bloody sputum or pleural pain with friction rub or signs of localized consolidation (infarction) by physical examination or roentgen-ray. There may also be a delayed appearance of a phlebitis in the leg responsible for the pulmonary embolism, or such a lesion may be found before the accident or at the time.

One of the peculiarities of pulmonary embolism, postoperative or otherwise, is that it is very likely to recur, sometimes frequently over a period of weeks. Such recurrence at frequent or short intervals is rare in the case of coronary thrombosis, and should at once put us on our guard about the diagnosis.

5. *Roentgen-Ray Evidence.* There exists as yet no roentgen-ray evidence of the acute cor pulmonale. It is difficult to obtain such evidence and we have yet to try to get it. We expect that when films are secured at the height of the trouble they will probably show in oblique or lateral views bulg-

ing anteriorly of the engorged right ventricle, and in anteroposterior views prominence of the pulmonary artery and of the right ventricular infundibulum, just below it and in some cases an increased transverse cardiac diameter mainly the result of dilatation of the right auricle.

So far as the pulmonary infarction is concerned roentgen-ray evidence as already noted above is often lacking at the first during the acute stage, but when it does develop it is naturally of fundamental diagnostic importance.

6. *Electrocardiographic Evidence.* Finally, to prove perhaps most important of all, is the electrocardiogram of the acute cor pulmonale. At the beginning of our study this was a source of confusion. The changes were slight but misleading, consisting of lowering, flattening, or even slight inversion of the T-waves in Lead II, inversion of the T-waves in Lead III, wide or deep S-waves in Lead I and inversion of QRS waves in Lead III. The records suggested those found with small areas of infarction at the base of the left ventricle behind due to occlusion of the right coronary artery—the so-called coronary T_3 type. With the subsidence of the condition, however, the electrocardiograms quickly became normal. As time went on we began to take Lead IV, the chest lead, with right hand electrode applied to the precordium midway between sternum and nipple line. To our surprise we found in this record an upright T-wave with relatively normal P and QRS waves, with return to normally inverted T-waves when the acute cor pulmonale subsided. The points of particular interest about this record are that it differs from the Lead IV of coronary thrombosis of either of the common (that is, T_1 or T_3) types, and that it is in agreement, so far as the T-wave is concerned at least, with Lead IV in mitral stenosis or the tetralogy of Fallot where the right ventricle is known t be enlarged. It is too soon as yet to state whether or not Lead IV of the electrocardiogram will prove to be the pathognomonic sign of the acute cor pulmonale. Many more records are needed.

In the *differential diagnosis* of the acute cor pulmonale the four conditions that are to be particularly considered are coronary thrombosis, dissecting aortic aneurysm, pulmonary collapse, or spontaneous pneumothorax, and pulmonary edema from heart disease with or without cardiac asthma. Only the first and last are both common enough and difficult enough to require special consideration, and such consideration of coronary thrombosis I have given in my discussion above on diagnosis. An additional point of importance favoring the diagnosis of coronary thrombosis is a past history of angina pectoris present in about half the cases. Finally, as an acute emergency pulmonary edema with or without cardiac asthma may simulate severe pulmonary embolism. The absence of any evidence of important heart disease before the attack, in the form of aortic valve disease, hypertensive heart disease, recent coronary thrombosis, or marked mitral stenosis helps to rule out pulmonary edema of cardiac origin and cardiac asthma.

Treatment. The treatment of the acute cor pulmonale is, in part, that

of the underlying disease, namely pulmonary embolism, which in very severe cases may necessitate the attempt at pulmonary embolectomy. In somewhat doubtful cases, before proceeding with this serious operation, it should prove very helpful to obtain further confirmation of the diagnosis by the finding of various signs of the acute cor pulmonale that I have presented above. Whether or not digitalis may be helpful in supporting the right ventricle in its strenuous work in these cases I do not know; I see no reason why it should not be given in fairly full but not toxic doses. Much time may elapse before we can obtain accurate information on this point. Venesection, when there is not a state of shock, may also be worth consideration in selected cases.

Literature. Only a few words need be said about the literature on this subject. So far as I know the first mention of the clinical recognition of the acute cor pulmonale, though not called by that name, was in a paper published by Oscar Brenner and myself [1] in the *New England Journal of Medicine* on December 21, 1933. A fairly full discussion of the subject, under the title of "The Acute Cor Pulmonale," by Sylvester McGinn and myself [2] has just appeared in the *Journal of the American Medical Association.* Otherwise one finds in the literature accounts of animal experimental work on occlusion of the pulmonary circulation and its effects, as by Cohnheim,[3] Mann,[4] Haggart,[5] Moore and Binger,[6] Churchill,[7] and their associates, brief references, at increasingly shorter intervals now, concerning the difficulties of differential diagnosis clinically between coronary thrombosis and pulmonary embolism, best exemplified by recent papers of Hamburger,[8] of Averbuck,[9] and of Hamman,[10] without especial reference, however, to the acute cor pulmonale, and finally a mention of some of the individual signs as by Litten [11] and Lord.[12] I hope that we have now somewhat clarified this difficult question.

Conclusion

The clinical recognition of the acute cor pulmonale—dilatation of the pulmonary artery and right heart chambers with or without failure—is an important step in the early differentiation between massive pulmonary embolism and coronary thrombosis or other conditions. Such recognition is of great importance in ultimate prognosis and may have significant bearing on emergency treatment. Evidence of the acute cor pulmonale has been presented above from the analysis of 14 cases.

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EFFECT OF VIBRATORY STIMULATION ON THE NEUTROPHILIC INDEX *

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While studying blood smears during the experimental production of eosinophilia,[1] the authors observed that electrical stimulation caused marked alteration in the character of neutrophiles in the circulating capillary blood. This stimulation produced an increase in the percentage of young neutrophiles which was relative and absolute.

According to Arneth,[2] the neutrophiles in the peripheral blood can be differentiated. He described several classes which are based on the theory of the successive development of a greater segmentation of the nucleus with age. Cooke and Ponder [3] have simplified this classification by establishing five major groups or types; the first being the youngest, and the fifth, the oldest circulating neutrophile. In their Type I neutrophile, the several parts of the nucleus are connected by a band of chromatin wider than a filament. The Type II neutrophile has a filament connecting two nuclear lobes. Type III is characterized by three lobes with connecting filaments. Type IV has four lobes with connecting filaments, and Type V has five or more lobes and uniting filaments. Their normal 'neutrophile formula' is as follows:

Type I	II	III	IV	V
10	25	47	16	2

The figures represent the numbers of each form in 100 circulating neutrophiles.

Emphasis has been placed by Schilling [4] on the clinical interpretation of this 'neutrophile formula.' An increase of the first two types, particularly the first, and a decrease of the others constitute the "shift to the left" which is peculiar to certain infections. Depending upon the extent of the "shift to the left," the severity of some infectious diseases and their prognoses can be estimated.

For electrical stimulation, we used induced current having a rate of 3600 vibrations per minute. The electrodes were firmly held in the hands and the intensity of the shocks was felt in the entire forearm. The period of stimulation was four minutes.

In each experiment, blood smears were taken immediately before, at the end of the stimulation period, 15 minutes later and lastly 30 minutes after stimulation.

Table 1 presents the total leukocyte counts, differential counts, and the Cooke and Ponder formulae of nine normal and of one abnormal young male

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adult. All these determinations were made between two and three o'clock in the afternoon. The leukocyte and differential counts were ascertained in the usual ways. The classification of the several neutrophiles was obtained by examination of especially stained specimens.

TABLE I

	Total WBC	% Polynuclears	% Type I (Arneth)	% Type II (Arneth)	% Type III (Arneth)	% Type IV (Arneth)	% Type V (Arneth)	% Large Lymph.	% Small Lymph.	% Monocytes	% Transitionals	% Basophiles	% Eosinophiles	Absolute No. Type I per cu. mm.
Pt. 1 Normal	8350	83	8.3	17.7	36.0	18.0	4.0	4.0	14.6	4.3	0.0	0.0	0.0	69
4′ Stimulation	9350	66.3	26.7	16.6	12.6	7.7	2.7	10.6	12.6	7.7	1.3	2.0	4.0	2506
15′ Later	9000	71.0	19.7	26.0	16.7	7.3	1.3	8.0	14.6	6.0	0.0	0.0	0.6	1773
30′ Later	8600	74.0	18.0	26.0	20.0	8.0	2.0	6.0	10.6	3.3	0.0	0.0	2.0	1548
Pt. 2 Normal	9000	60	4.0	10.0	20.0	22.0	4.0	14.0	16.7	4.3	5.7	0.6	2.0	360
4′ Stimulation	11450	63	16.0	20.0	15.0	10.0	2.0	12.0	19.0	7.0	4.0	0.0	1.0	1832
15′ Later	10200	68	6.0	16.0	24.0	16.0	6.0	13.0	12.0	1.0	4.0	0.0	1.0	612
30′ Later	9800	70	4.0											392
Pt. 3 Normal	5650	70	2.0	10.0	24.0	23.8	10.2	6.7	13.3	4.6	4.6	0.0	1.7	113
4′ Stimulation	7150	65.5	12.5	18.0	20.0	13.0	2.0	10.5	15.0	5.5	2.0	0.0	0.0	894
15′ Later	6800	70	10.0	14.0	22.0	20.0	4.0	6.7	13.3	4.3	0.7	0.0	1.7	680
30′ Later	6400	73	7.0											448
Pt. 4 Normal	8200	54.14	0.68	7.16	31.4	13.6	1.3	6.12	27.9	3.7	0.34	0.0	1.02	56
4′ Stimulation	10800	66.5	19.0	22.5	23.5	3.5	0.0	7.0	19.0	3.5	0.0	0.0	2.5	2052
15′ Later	9600	54.2	8.4	20.1	29.2	6.5	0.0	9.1	18.2	3.9	1.3	0.0	2.5	806
30′ Later	9200	64.7	6.68	18.42	28.6	8.4	2.1	6.8	20.4	3.8	1.0	0.0	4.1	614
Pt. 5 Normal	6600	74.6	1.53	12.2	41.3	18.3	1.5	3.1	12.2	6.1	1.5	0.0	1.5	101
4′ Stimulation	8400	75.35	19.90	20.0	24.8	9.85	0.8	1.65	11.4	8.6	2.8	0.0	0.0	1670
15′ Later	8000	76.54	10.34	14.84	34.78	16.58	0.0	2.7	12.56	4.8	2.1	0.0	1.0	827
30′ Later	7400	77.77	8.60	13.42	34.8	18.52	2.4	3.0	10.8	4.0	2.0	0.0	1.0	636
Pt. 6 Normal	5000	43.8	0.6	6.6	20.0	10.0	6.6	13.3	33.0	10.6	10.0	0.6	1.3	30
4′ Stimulation	5750	60.2	10.0	19.6	16.0	10.6	4.0	10.6	10.6	8.0	10.0	0.0	1.3	575
15′ Later	5600	50.3	5.0	9.6	23.8	14.7	7.2	11.0	7.8	6.8	11.0	0.0	1.8	280
30′ Later	5200	61.0	4.0	8.0	30.0	12.0	7.0	8.0						208
Pt. 7 Abnormal	14200	7.4	0.0	2.8	3.7	0.9	0.0	6.5	15.3	0.9	0.9	0.0	69.0	0
4′ Stimulation	15000	6.5	2.8	2.8	0.9	0.0	0.0	2.7	6.3	2.8	2.8	0.9	77.0	420
15′ Later														
30′ Later														
Pt. 8 Normal	7600	68.4	1.6	17.1	35.7	10.5	3.5	7.2	18.7	1.7	1.5	1.0	1.5	122
4′ Stimulation	9100	61.8	9.53	17.65	25.72	8.9	0.0	5.15	22.8	8.82	1.54	0.0	0.0	870
15′ Later	8800	62.75	7.8	19.65	24.8	9.0	1.5	6.0	24.0	6.4	1.5	0.0	0.0	686
30′ Later														
Pt. 9 Normal	8600	72.2	6.2	16.4	32.6	14.2	2.8	2.2	15.8	1.0	1.2	0.0	0.0	533
4′ Stimulation	10400	63.0	16.4	18.2	22.3	4.5	1.6	7.3	11.4	8.2	6.4	1.5	0.0	1712
15′ Later	9800	70.3	12.1	22.0	27.2	7.0	2.0	7.2	14.4	4.6	2.0	1.0	0.0	1186
30′ Later	9200	71.8	9.2	21.6	30.4	8.2	2.4	7.0	15.4	3.2	1.5	1.1	0.0	846
Pt. 10 Normal	8400	75.4	0.8	10.0	41.0	12.6	1.0	3.0	26.0	3.0	3.0	0.0	0.0	7
4′ Stimulation	10800	75.6	20.6	18.0	29.0	7.0	1.0	9.0	11.0	3.5	3.0	0.0	0.0	2225
15′ Later	9600	81.3	14.2	20.6	30.0	14.0	2.5	4.0	13.0	2.0	1.0	0.0	0.0	1363
30′ Later	8800	79.6	9.4	24.2	28.0	12.0	6.0	3.0	16.0	1.5	0.5	0.0	0.0	827
Average (Normal)	7710	67.17	2.88	10.99	28.57	14.39	3.49							132
4′ Stimulation	9240	66.47	16.74	17.33	18.98	7.51	1.41							1593
15′ Later	8600	67.15	10.38	18.08	25.73	12.42	2.45							912
30′ Later	8075	71.48	7.86	18.60	28.63	11.20	2.34							689

Study of the averages in table 1 reveals that before stimulation only 132 of the 5179 neutrophiles are of the first or youngest type. Immediately after stimulation there is only an increase of 1500 neutrophiles of all types, whereas there is an absolute increase of 1461 Type I neutrophiles. The difference must represent older leukocytes which have been either removed from the circulating blood or greatly dispersed by the influx of the younger forms.

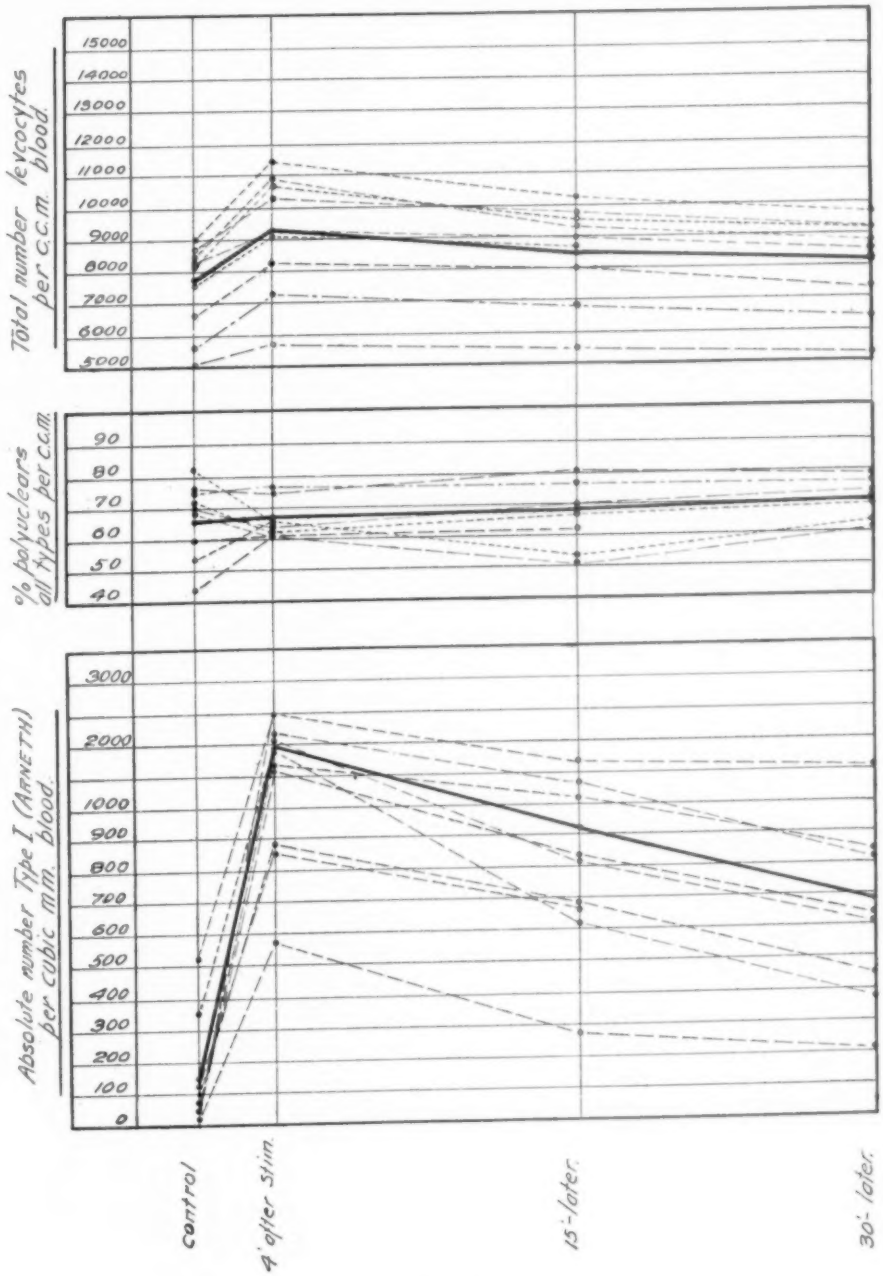
Total number leucocytes per c.c.m. blood
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
% polynuclears all types per c.c.m.
90
80
70
60
50
40
Absolute number Type I (Arneth) per cubic mm. blood
3000
2000
1000
900
800
700
600
500
400
300
200
100
0
control
4' after Stim.
15'-later.
30'-later.

FIG. 1

That is, at least 1461 young neutrophiles have appeared suddenly in each cubic millimeter of peripheral blood and displaced the older forms. Table 1 also demonstrates a similar absolute and relative increase of Type II neutrophiles, but the change is not so striking.

Blood analyses of several subjects showed that the Type I neutrophilia persisted for several days. Three had a Type I neutrophile increase of 3 to 5 per cent above the original count for 4 days. Furthermore, it was found that when these individuals were re-stimulated, the Type I neutrophilia at the end of four minute stimulation exceeded that of the first day by 10 to 12 per cent.

Figure 1 demonstrates graphically the type of curve following stimulation with induced current. Even though the total leukocyte count and the absolute number of Type I neutrophiles rise and fall sharply, the differential count line remains practically flat.

Comparison of the results obtained by electrical stimulation with the effects of mechanical vibration was next investigated. For this purpose, two commercial massage vibrators were utilized—one with a rate of 4200 vibrations per minute, and the second with a rate of 7200 per minute. The subjects, by tightly grasping the vibrating instrument, were stimulated four minutes.

In table 2 are tabulated the blood changes resulting from mechanical stimulation with a rate of 4200 vibrations per minute. The same technic was followed as outlined in table 1. With this vibrator the average increase of total leukocytes was 38.8 per cent and the increase of neutrophiles of all types was 3.17 per cent. There was an absolute increase of 11.44 per cent Type I neutrophiles. Figure 2 graphically shows these changes.

TABLE II

	Total WBC	% Polynuclears	% Type I (Arneth)	% Type II (Arneth)	% Type III (Arneth)	% Type IV (Arneth)	% Type V (Arneth)	% Large Lymph.	% Small Lymph.	% Monocytes	% Transitionals	% Basophiles	% Eosinophiles	Absolute No. Type I per cu. mm.
Pt. 1 Control	8600	50.05	1.45	10.80	29.7	8.1	0.0	10.8	28.4	2.7	6.7	0.0	1.3	124
4′ Stimulation	10200	66.65	17.5	18.65	24.1	4.4	0.0	7.68	19.9	4.4	3.2	0.0	0.0	179
15′ Later	9860	55.11	9.73	17.7	16.81	9.9	1.0	7.96	21.8	7.08	7.1	0.0	1.0	960
30′ Later	9600	74.12	5.62	24.7	31.5	10.1	2.2	3.37	17.0	2.25	2.25	0.0	0.0	540
Pt. 2 Control	7600	66.4	0.0	19.7	29.2	14.0	3.5	5.3	20.1	3.5	3.5	1.0	1.75	0
4′ Stimulation	11200	70.7	12.5	17.5	29.7	9.5	1.5	6.5	17.5	5.0	2.5	0.0	0.0	1400
15′ Later	9800	68.3	6.85	21.7	32.14	7.6	0.0	6.0	18.3	4.0	2.2	0.0	1.0	761
30′ Later	8000	71.6	5.65	22.4	28.2	9.2	1.5	5.15	21.2	5.0	1.5	0.0	0.25	452
Pt. 3 Control	6400	62.7	2.2	16.1	23.8	18.6	2.0	8.6	20.2	4.2	3.8	0.0	0.5	141
4′ Stimulation	9200	59.5	10.6	18.0	17.6	12.8	0.5	11.4	16.6	8.6	2.4	0.5	1.0	975
15′ Later	8000	65.8	8.8	21.0	20.8	14.2	1.0	9.2	16.0	6.7	1.3	0.0	1.0	704
30′ Later	8400	67.9	6.8	23.0	21.2	14.9	2.0	4.8	20.1	3.2	3.0	0.0	1.0	571
Pt. 4 Control	6800	61.7	1.0	20.6	23.5	14.6	2.0	8.2	21.6	3.6	4.4	0.5	0.0	68
4′ Stimulation	10200	59.3	9.8	23.6	16.5	8.9	0.5	10.2	18.6	6.9	3.0	1.0	1.5	999
15′ Later	8800	60.4	6.4	23.4	18.9	10.2	1.5	8.8	20.6	3.8	4.5	1.0	1.0	563
30′ Later	9000	69.1	6.0	24.2	22.1	14.8	2.0	8.2	22.0	3.2	5.0	1.0	1.5	540
Average	7350	60.21	1.16											84
	10200	64.04	12.6											888
	9115	62.40	7.94											747
	8750	70.68	6.02											526

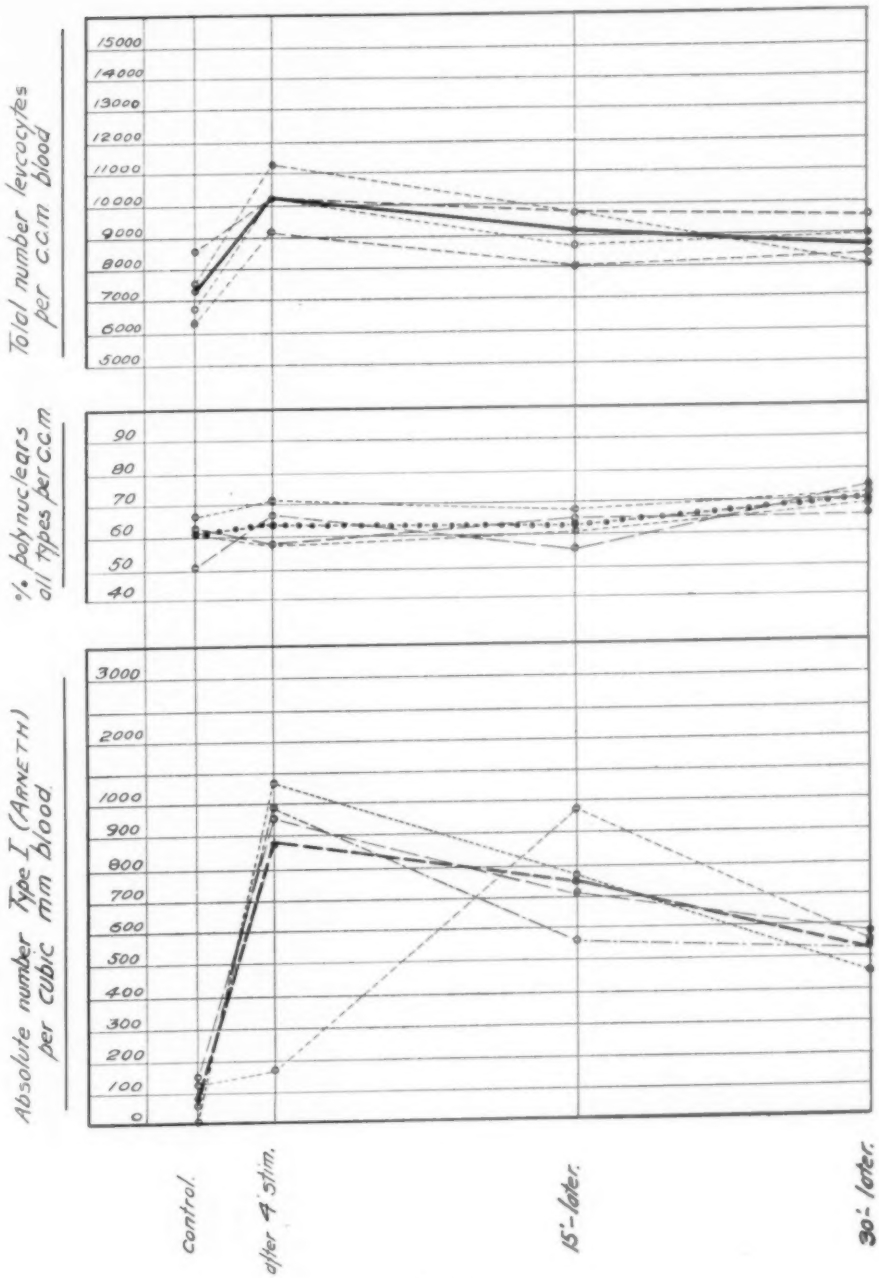
Total number leucocytes per ccm blood
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
% polynuclears all types per ccm
90
80
70
60
50
40
Absolute number Type I (Arneth) per cubic mm blood
3000
2000
1000
900
800
700
600
500
400
300
200
100
0
Control.
after 4' stim.
15'- later.
30'- later.

FIG. 2

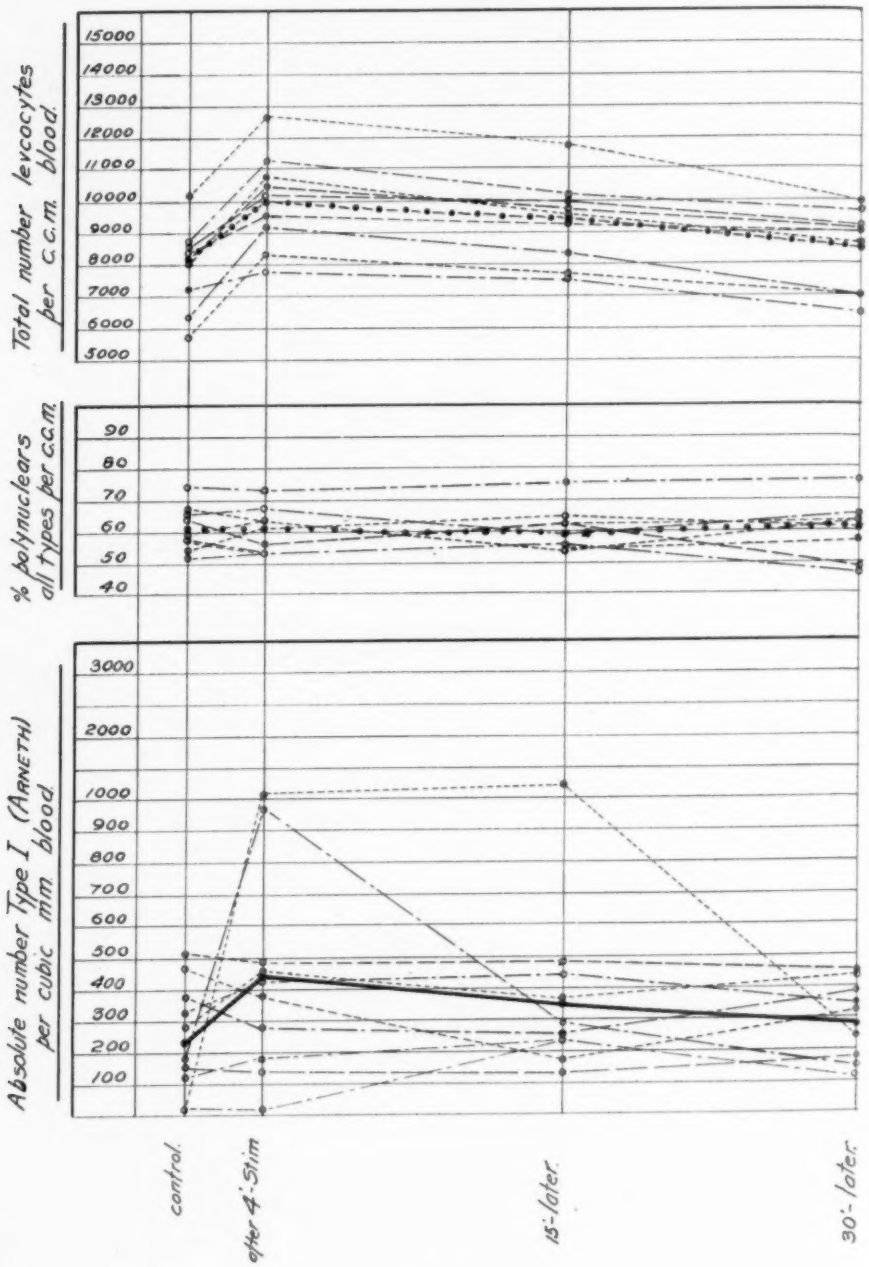
Total number leucocytes per c.c.m. blood
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
% polynuclears all types per c.c.m.
90
80
70
60
50
40
Absolute number Type I (Arneth) per cubic mm blood
3000
2000
1000
900
800
700
600
500
400
300
200
100
control.
after 4'-Stim
15'-later.
30'-later.

FIG. 3

In table 3 are the results obtained by the use of the second instrument whose rate was 7200 vibrations per minute. Stimulation was applied in the same way as in the preceding experiments and the specimens were collected in an identical manner. The table shows that the total white count is elevated 25.2 per cent and the polynuclear percentage is slightly less than the control. In these respects, the results of the experiment are nearer to those obtained by the induced current. However, the 1.18 per cent increase of Type I neutrophiles shows that it is the least efficient instrument used.

Figure 3 demonstrates curves which conform generally to the two previous figures. The amplitude of the curves, however, is less prominent.

TABLE III

	Total WBC	% Polynuclears	% Type I (Arneth)	% Type II (Arneth)	% Type III (Arneth)	% Type IV (Arneth)	% Type V (Arneth)	% Large Lymph.	% Small Lymph.	% Monocytes	% Transitionals	% Basophiles	% Eosinophiles	Absolute No. Type I per cu. mm.
Pt. 1 Control	8700	58.2	1.94	14.55	21.34	17.46	2.91	4.85	32.01	1.94	2.91	0.85	0.0	169
4′ Stimulation	11400	54.1	8.48	16.96	22.26	5.30	1.06	5.30	31.80	2.12	4.24	1.06	0.0	967
15′ Later	10200	57.7	2.92	13.94	27.00	12.40	1.45	5.83	29.92	3.64	1.46	0.0	2.1	298
30′ Later	9800	47.7	1.58	11.06	23.07	7.90	3.16	4.74	30.02	12.64	1.58	0.0	0.0	155
Pt. 2 Control	8600	55.3	5.53	4.74	31.6	11.85	1.58	6.32	23.7	3.95	1.79	0.95	9.48	476
4′ Stimulation	10200	60.25	3.75	14.0	31.25	10.0	1.25	5.6	16.0	6.75	2.0	0.0	6.80	383
15′ Later	10000	62.69	1.81	11.81	31.81	15.45	1.81	5.43	17.24	2.67	2.72	0.8	5.43	181
30′ Later	9200	61.94	3.44	12.90	29.09	17.41	1.1	1.8	20.69	4.5	3.0	0.3	6.0	317
Pt. 3 Control	8400	63.54	1.54	8.10	32.6	16.3	4.96	3.78	23.3	2.70	0.6	0.0	0.6	129
4′ Stimulation	9600	56.62	1.95	13.58	24.09	14.4	2.6	6.46	36.36	1.29	0.65	0.0	0.65	187
15′ Later	9400	61.07	2.59	16.83	28.4	18.75	4.5	4.5	30.5	3.09	4.1	2.0	2.1	243
30′ Later	9000	62.84	2.26	13.3	31.51	12.77	2.26	2.26	29.0	4.5	4.5	0.0	1.5	103
Pt. 4 Control	10200	65.13	0.0	14.5	33.01	16.03	0.94	6.60	23.85	1.88	0.94	0.0	1.88	0
4′ Stimulation	12600	67.37	9.3	26.74	22.03	9.3	0.0	3.48	20.8	1.60	3.48	0.0	3.48	1072
15′ Later	11800	59.90	10.56	20.32	23.65	4.87	0.5	4.87	19.51	7.31	4.06	0.5	2.43	1246
30′ Later	10000	64.0	2.4	17.6	28.0	13.6	2.4	5.2	19.2	8.00	1.6	0.0	1.60	240
Pt. 5 Control	5800	67.33	0.0	10.04	29.17	26.04	2.08	2.08	15.62	6.24	3.10	0.0	5.2	0
4′ Stimulation	8400	63.43	0.0	9.52	31.74	19.0	3.17	4.76	17.46	4.76	4.76	0.0	3.17	0
15′ Later	7600	55.87	0.0	6.49	26.0	19.48	3.90	10.4	24.6	3.9	2.6	0.0	2.6	0
30′ Later	7000	64.68	3.4	13.6	31.81	10.20	5.67	3.4	20.4	9.09	2.27	0.0	0.0	238
Pt. 6 Control	8000	59.00	4.0	11.0	31.0	11.0	2.0	3.0	21.0	10.0	3.0	0.0	4.0	320
4′ Stimulation	10800	64.00	4.0	17.0	32.0	11.0	0.0	5.0	15.0	6.0	3.0	1.0	1.0	432
15′ Later	9600	59.15	4.62	14.8	31.4	8.33	0.0	8.4	27.7	5.5	1.0	0.0	0.6	444
30′ Later	8800	49.14	3.82	12.9	26.0	3.82	2.6	6.4	31.0	5.2	5.2	1.3	1.3	336
Pt. 7 Control	8600	73.37	6.02	12.04	33.13	22.28	4.2	2.8	12.05	4.2	1.2	0.0	1.2	518
4′ Stimulation	10200	73.26	4.80	12.6	29.36	21.4	5.1	3.1	15.8	3.1	1.6	0.0	2.6	490
15′ Later	9480	74.2	5.20	13.4	28.0	23.0	4.6	3.4	14.2	4.5	2.0	0.8	2.0	493
30′ Later	9000	75.9	5.10	12.8	30.4	23.6	4.0	4.2	16.4	3.0	1.5	0.0	1.5	459
Pt. 8 Control	7200	52.65	2.7	6.75	21.6	13.5	8.1	2.7	32.4	8.1	2.7	0.0	2.7	194
4′ Stimulation	7800	53.0	2.0	5.0	25.0	15.0	6.0	6.0	31.0	7.0	1.0	1.0	1.0	156
15′ Later	7600	54.0	2.0	5.0	27.0	15.0	5.0	5.0	29.0	9.0	3.0	1.0	3.0	152
30′ Later	6500	57.25	2.9	8.7	23.2	20.3	2.15	5.8	26.1	5.1	1.7	0.7	1.7	186
Pt. 9 Control	6400	58.84	4.51	9.02	27.1	13.7	4.51	10.6	27.1	4.51	4.4	0.0	0.0	289
4′ Stimulation	9200	55.0	5.0	12.0	23.0	12.0	3.0	7.0	30.0	6.0	0.0	0.0	1.0	460
15′ Later	8400	54.9	4.60	11.2	24.0	12.6	2.5	8.0	29.0	5.4	2.0	0.0	0.7	386
30′ Later	8000	64.9	5.50	8.7	22.0	5.5	3.2	10.9	32.9	5.5	5.5	0.0	0.0	440
Pt. 10 Control	8200	59.74	4.54	16.6	18.0	15.1	5.5	0.8	23.2	10.6	4.5	0.0	0.0	372
4′ Stimulation	10400	60.21	2.71	6.7	26.8	20.0	4.0	6.7	16.0	9.4	2.7	0.0	4.0	282
15′ Later	9700	59.4	2.7	9.0	26.0	19.8	1.9	3.6	22.4	9.7	2.7	0.0	2.8	262
30′ Later	9000	58.57	4.38	8.77	28.0	14.8	2.62	2.6	27.1	2.6	1.8	2.6	3.6	394
Pt. 10 (1 day later) Control	8600	68.47	5.97	14.9	26.1	18.6	2.9	5.22	26.1	2.2	1.1	1.1	3.7	514
4′ Stimulation	10200	64.46	9.9	18.26	20.6	11.6	4.1	5.4	20.9	5.0	1.1	0.0	2.4	1010
Av. 10 Pts. Control	8030	61.31	3.08											247
4′ Stimulation	10060	60.71	4.20											443
15′ Later	9378	59.88	3.70											371
30′ Later	8630	60.71	3.48											286

The results of stimulating the hands and forearms of five elderly people (over 70 years of age) are recorded in table 4. Figure 4 represents graphically the alteration of total white counts, polynuclear percentages, and

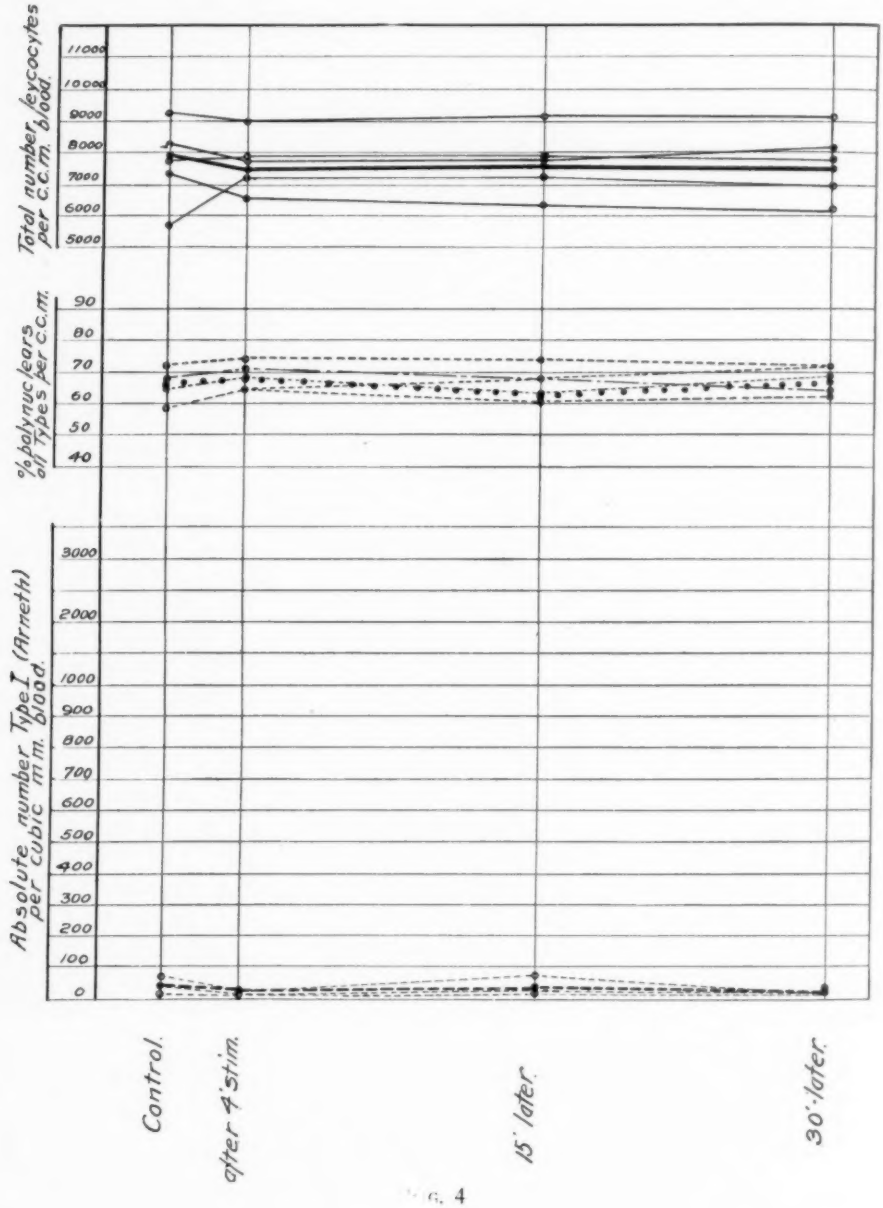

FIG. 4

changes in the absolute number of Type I neutrophiles. There is a sharp fall in the total number of white cells and the number of Type I neutrophiles immediately after stimulation and a slight rise 15 minutes later.

The weighted means of the Cooke and Ponder formulae are charted in figure 5. The line of the average weighted means of each experiment shows greatest deflection from the control in the lowest curve. There is a less marked deviation in the second and third curves. The fourth, corresponding to the weighted means taken from elderly subjects' blood, is practically

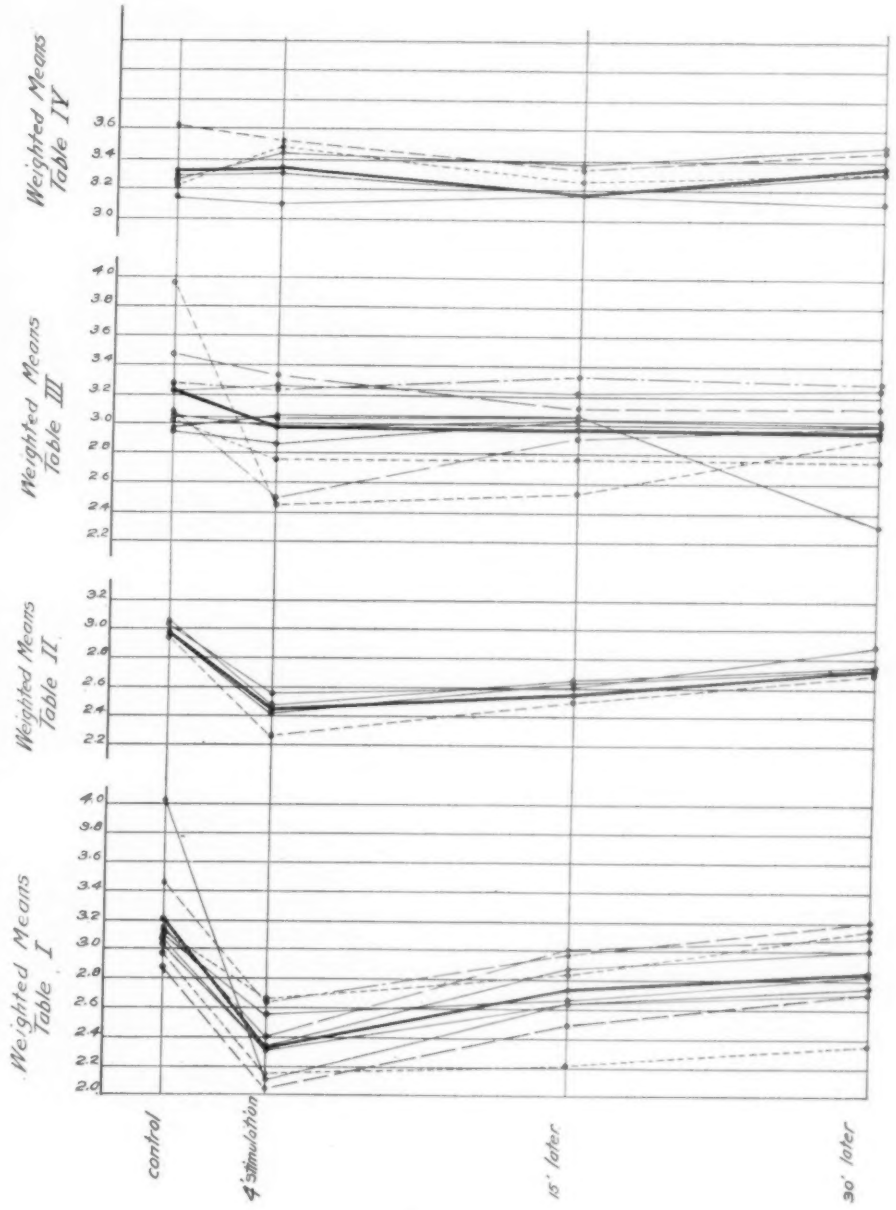

FIG. 5

TABLE IV

	Total WBC	% Polynuclears	% Type I (Arneth)	% Type II (Arneth)	% Type III (Arneth)	% Type IV (Arneth)	% Type V (Arneth)	% Large Lymph.	% Small Lymph.	% Monocytes	% Transitionals	% Basophiles	% Eosinophiles	Absolute No. Type I per cu. mm.
Pt. 1 Control	6850	72.4	0.0	7.4	48.0	14.0	3.0	4.0	21.0	2.0	0.6	0.0	0.0	0
4′ Stimulation	7200	73.1	0.0	6.8	48.2	16.0	2.1	3.8	20.0	1.5	0.6	0.0	0.0	0
15′ Later	7300	73.1	0.0	7.1	47.8	15.6	2.6	4.0	21.0	1.5	0.2	0.0	0.0	0
30′ Later	7000	71.7	0.8	8.2	46.5	14.2	2.0	3.6	22.0	2.0	0.5	0.0	0.2	6
Pt. 2 Control	8200	68.8	0.8	8.0	36.0	20.0	4.0	2.2	26.5	1.5	0.0	0.0	1.0	7
4′ Stimulation	7800	70.7	0.5	6.8	38.0	22.0	3.4	1.8	26.0	1.0	0.5	0.0	0.0	4
15′ Later	7850	68.4	1.2	9.4	36.0	19.0	2.8	2.0	28.0	1.5	0.0	0.0	0.1	84
30′ Later	8100	71.1	0.6	4.2	39.0	23.5	3.8	1.0	27.0	0.5	0.0	0.0	0.4	5
Pt. 3 Control	9400	59.0	1.4	6.8	29.6	18.0	3.2	4.0	27.0	4.6	5.1	0.3	0.0	13
4′ Stimulation	9000	65.6	0.6	4.3	32.8	21.5	6.4	3.8	28.0	1.6	1.0	0.0	0.0	5
15′ Later	9200	68.6	1.0	5.0	34.0	23.0	5.0	4.2	25.0	2.0	0.8	0.0	0.0	9
30′ Later	9200	64.2	1.2	6.0	34.5	22.5	4.0	4.0	28.0	2.0	1.8	0.0	0.0	11
Pt. 4 Control	7400	66.4	0.8	4.5	30.5	24.6	6.0	3.0	25.0	3.0	2.0	0.0	0.6	60
4′ Stimulation	6600	68.3	0.0	3.8	31.0	26.0	7.5	4.0	28.0	3.5	3.5	0.0	1.4	0
15′ Later	6400	63.0	1.6	6.2	27.0	23.4	4.8	3.6	27.6	4.0	1.5	0.0	0.3	10
30′ Later	6200	69.0	1.2	5.4	30.0	26.0	6.4	4.2	25.8	1.0	0.0	0.0	0.0	7
Pt. 5 Control	7800	58.9	2.5	8.8	24.8	18.6	4.2	5.0	31.5	3.0	1.0	0.0	0.6	18
4′ Stimulation	7850	65.3	1.8	6.5	31.0	20.0	6.0	4.5	30.0	0.2	0.0	0.0	0.0	14
15′ Later	7900	61.8	2.2	7.6	27.0	20.0	5.0	5.5	29.0	2.0	1.0	0.0	0.7	17
30′ Later	7800	62.6	2.4	8.0	26.0	20.0	6.2	4.8	27.0	3.0	1.0	0.0	0.8	19
Average Control	7930	65.1	0.9	7.1	33.8	19.0	4.1							20
4′ Stimulation	7690	68.6	0.6	5.6	36.2	21.1	5.1							5
15′ Later	7730	62.9	1.2	7.1	34.3	20.2	4.0							24
30′ Later	7660	67.7	1.4	6.3	35.2	21.4	4.5							8

flat. Induction current stimulation appears to be the most efficient means of deviating the index to the left in young people.

DISCUSSION

By means of induction current and mechanical vibration, the normal neutrophilic formula can be quickly altered. This change is identical to the "shift to the left" which has been reported in severe infectious diseases. An important difference, however, is that there were no basophilic granules in the cytoplasm of the neutrophiles of any type before or after the shift had occurred. By means of Jenner-Giemsa staining, Kugel and Rosenthal [5] have studied the blood smears of people who had not only a marked "shift to the left" but also a preponderance of basophilic granular neutrophiles in infections with poor prognoses. In our experiments, the "shift to the left" was prominent, but we failed to detect the signs of cytoplasmic degeneration with unfavorable prognoses as reported by the above authors. Furthermore, the alteration of the hemograms by our experimental procedure failed to elicit symptoms or signs of a physical abnormality in any subject.

The mechanism of this "shift to the left" cannot be explained at this time. A similar alteration of the hemogram has been produced by others using chemical and physical agents. Kennedy and Thompson [6] have produced a "shift to the left" in the Arneth index of animals irradiated with ultra-violet light. A similar change was obtained by the feeding of irradiated ergosterol to rabbits.[7] Danzer [8] has demonstrated that the destruction

and absorption of tissue in vivo is followed by a deflection of the Arneth index. He has suggested that the continual and normal breakdown of body tissue provides a stimulus for the normal output of neutrophiles by the bone marrow.

Study of the above tables reveals an immediate loss of the older neutrophiles after induction current or mechanical vibratory stimulation. Destruction of these older cells liberates nucleic acid and its derivatives which have a definite effect on the myeloid foci.[9]

The adenine sulphate content of the blood before and after stimulation is at present being analyzed in this laboratory. From the evidence to date, there is no relationship between the "shift to the left" and the nucleotide content.

Conclusions

1. The proportion of young to old neutrophiles in the peripheral blood may be reversed by induction current and vibratory stimulation of the extremities.

2. The "shift to the left" is only a temporary phenomenon in this experimental procedure, but it may be retained for several days by repeated stimulation without detrimental effects.

3. Basophilic granular degeneration of the neutrophilic cytoplasm does not occur with this "shift to the left."

4. "Shift to the left" by itself is not exclusively a sign of severe infection.

5. The production or distribution of young neutrophiles is markedly decreased in senile conditions.

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A STUDY OF 118 READMISSIONS TO OAKHURST SANATORIUM OF GRAYS HARBOR COUNTY, WASHINGTON *

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EVERY tuberculosis sanatorium, especially if it is tax supported, has its more or less large quota of readmissions, and yet one does not often see in medical literature studies of such statistics with efforts to account for relapses or other conditions requiring readmission. A careful consideration of such data by the staff of each sanatorium should yield valuable information and in time might help to correct some of the inherent difficulties.

The present statistics relate to Oakhurst Sanatorium at Elma, Grays Harbor County in the State of Washington. The institution is owned and maintained by the county which has an area of 1869 square miles and a population of about 60,000. It accepts only patients who have resided in the county for one year.

The data analyzed cover a period of 12 years and 9 months, from the opening of the institution in August 1921 with 22 beds, to May 31, 1934 when there were 68 beds. The records of non-tuberculous patients have been excluded from the study and also cases of the childhood type of tuberculosis because, in the latter instance, some of the earlier diagnoses would not agree with the present conception of that type of the disease. No apology is offered for the few cases presented. They represent a problem that must be met in many small institutions throughout the country where the staff is very limited and where there are not the facilities or equipment of the large well organized sanatorium, to say nothing of the extensive follow-up system so necessary for supervision of the discharged patient.

The writer, as medical director of the sanatorium, had in effect a definite program of education of the patient which began with his admission and continued throughout his stay. This was carried out by a course of reading of books on tuberculosis written especially for the laity and it was constantly supplemented by talks by the physician and the chief nurse. The patient was encouraged to ask questions regarding the general subject of tuberculosis and especially about his own condition. Except in the case of those gravely ill with tuberculosis, it is essential that the patient be given some insight into his condition in order that he may make his plans accordingly.

On the occasion of the first examination, considerable time was taken to discuss the patient's condition with him. He was told enough of the findings (physical and roentgen-ray) so that he might get an understanding of what was to be expected. It is always a problem to decide how much to tell the patient lest he overestimate his condition on the one hand or under-

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rate it on the other. It seems obviously wrong to tell him too many details and to be too confident in venturing a prognosis. A compromise must be sought in each case.

At the time that the patient was started on the more active exercise phase of his treatment a more intensive educational program was pursued. He was encouraged to assume more and more responsibility in his own care so that at the time of his discharge he was virtually on his own responsibility. At the same time, the relatives and friends were interviewed by the physician and the patient's condition carefully reviewed and a plan of living at home outlined. It was clearly set forth just what the patient might do and what he ought not to do. Emphasis was placed upon the fact that the appearance of health and splendid physique did not justify a rapid return to former pursuits and occupation. The patient's first month at home was so planned that he would not be taking nearly as much exercise as he was taking at the sanatorium. He was warned to avoid fatigue and to endeavor to keep away from those affected with transmissible diseases, especially infections of the upper respiratory tract. He was cautioned against the use of alcohol and dissipation of any kind and advised not to return to smoking. Long trips, especially by automobile, and late hours were forbidden. He was given an appointment to return for examination in approximately one month after discharge.

Each patient on discharge was given a mimeographed sheet of instructions. He was reminded not to pay attention to the opinions of friends and relatives about his condition and what he should do. He was urged to write or to telephone to the sanatorium when in doubt.

As an addendum to this study a brief review will be given showing in a period of four years how well patients responded to the request to return for reëxamination.

The statistics to be presented concern 118 discharged patients who required readmission one to four times during the period previously mentioned (August 1921 to May 31, 1934).

TABLE I

Length of Stay in Sanatorium	1st Readm.	2nd Readm.	3rd Readm.	4th Readm.
Less than 1 mo.	5			
1–2 mo.	15	3		
3–5 mo.	29	7	3	1
6–8 mo.	15	5	1	
9–11 mo.	5	4	3	
12–14 mo.	7	2	1	
15–17 mo.	3	2		
18–20 mo.	1			
21–23 mo.	0			
24–26 mo.	2			
36–38 mo.	1	1		1
48 mo.	1			
	84	24	8	2

In table 1 is shown the number readmitted and how long they stayed. For example: reading across, it is noted that of the patients who remained in the sanatorium three to five months, 29 were readmitted once, seven readmitted twice, three a third time, and one a fourth time. Further study of the table suggests that the longer a patient remained in the sanatorium the first time he was admitted, the less likely was he to have to be readmitted, and that after one readmission, the necessity for readmission became less. This is just as one would expect but it is frequently overlooked or forgotten when patients are considered ready for discharge. Often the physician's judgment is hampered by the intense desire that the patient has to go home. The mental condition of some patients is such that after a period of residence in a sanatorium they become restless and, in some instances, so homesick that they fail to give coöperation and if not discharged they either leave against medical advice or else adversely influence their fellow patients and, for the good of the institution, must be sent home.

Most sanatorium physicians are wont to urge an increase in residence in the institution to cover a long period after all symptoms and signs of active disease have disappeared as well as roentgen-ray evidence confirmatory of the same. Especially is this so if living conditions at home are poor and the patient has had a severe tuberculous infection or a low immunity. The limited bed capacity in public institutions where there is usually a long waiting list, and the financial limitations of the patient in a private sanatorium make this problem very difficult of solution and often it really leaves no choice to the medical superintendent when the situation arises.

TABLE II

Time Out of Sanatorium before Readmission

	1st Readm.	2nd Readm.	3rd Readm.	4th Readm.
Less than 1 mo.	10	5		
1–2 mo.	21	9	4	1
3–5 mo.	12	5	1	1
6–8 mo.	8	2	1	
9–11 mo.	6			
12–14 mo.	9	1	1	
15–17 mo.	2			
18–20 mo.	3			
21–23 mo.	1			
24–26 mo.	2	1	1	
30–32	2			
4 years	4			
5 years	2	1		
6 years	1			
7 years	1			
	84	24	8	2

The interpretation of table 2, reading across, for example, signifies that of patients who were out of the sanatorium less than two months, 10 were readmitted once, and five were readmitted twice. Most of those readmitted who were out of the sanatorium less than a month had left against medical advice or because of some emergency alleged to exist at home requiring their

presence. Sanatorium physicians are familiar with the type of patient who has been admitted with the idea that he would have to stay only a few weeks. His attending physician or his family may have told him this in order to get him to consent to hospitalization. He resents the apparent deception by refusing to stay. After he has returned home he becomes worse or he realizes his mistake and often wishes to be readmitted.

Sixty-nine patients had to be readmitted within five months of discharge, most of them within two months. This table would suggest that if the patient maintains himself well during the first six months out of the sanatorium, he stands an increasingly good chance of remaining well. The few relapses that occurred at four to seven years after admission were due largely to mechanical injuries of the chest, pregnancy or severe intercurrent chest infections such as pneumonia, influenza, etc.

TABLE III

Apparent Reason Requiring Readmission

1. Retrogression	12
2. Poor home conditions	20
3. Unavoidable (86 cases)	
a. Extension of infection to other lung or reactivation of original site	24
b. Pleuritis (without effusion)	3
c. Pleuritis with effusion	3
d. Thoracoplasty	24
e. Convalescence from laparotomy for tuberculous peritonitis	7
f. Tuberculous empyema	3
g. Tuberculous osteitis	4
h. Tuberculous laryngitis	1
i. Tuberculous kidney	1
j. Tuberculous enteritis	1
k. Operation for non-tuberculous conditions (duodenal ulcer, sinusitis, etc.)	4
l. Hemoptysis	8
m. Influenza	2
n. Pregnancy	1
	118

In table 3, by a careful review of each history, an effort has been made to determine the probable or apparent cause requiring readmission. Under "Retrogression" were included conditions for which the patient was largely responsible such as disregard of advice as to the proper mode of living (which might include carelessness as well as ignorance), over-exercise, alcoholic debauch and other forms of dissipation. It is surprising that so comparatively few come under this heading, there being only 12 (10 per cent). In two cases, influenza was believed responsible for reactivation of inactive disease and pregnancy was thought responsible for one case. "Poor home conditions" include poor housing with many steps to climb, overcrowding, deficient ventilation and light. It also includes the case of the housewife with a large family dependent on her. Twenty (17 per cent) were so classified.

The majority of those who had to be readmitted seemed to be victims of unavoidable conditions variously classified and not apparently due to the

fault of anyone. Thirty-one (36 per cent) of these were readmitted to convalesce from thoracoplastic operations or from laparotomy at which tuberculous peritonitis had been discovered.

In our series only eight cases (6.7 per cent) returned because of hemoptysis. In 16 instances (13.5 per cent) tuberculous complications of pulmonary tuberculosis required readmission. Evidently, in 86 (74.5 per cent) it was through no fault of the patient that he had to return to the sanatorium.

TABLE IV

Occupation

Nurse	1	Tile setter	1
Stenographer	3	Logger	9
Telephone operator	1	Carpenter	1
Teacher	3	Dancer	1
Housewife	40	Box factory worker	1
Common laborer	20	Abstractor	3
Student	19	Assistant postmaster	1
Laundry worker	1	Bricklayer	1
Barber	1	No occupation	10
			118

TABLE V

Social Condition and Sex

Single	41	Male	40
Married	60	Female	78
Divorced	11		118
Widowed	2		
Separated	4		
	118		

TABLE VI

Nationality

American	92
Swedish	3
Norwegian	1
Australian	3
Canadian	3
Finnish	10
Italian	1
Croatian	1
Scotch	1
Greek	1
American Indian	1
Welsh	1
	118

As to occupation, the housewife represented the larger group (40, or 33 per cent). It is difficult for the housewife to return to her home and maintain her good condition especially where there are small children or where relatives and friends interfere with her continuing to follow advice given on discharge. It is probable that statistics of other sanatoria would show likewise the greater frequency of relapse among housewives than

among other occupations. The same is shown in the tabulation of social condition and sex where 41 (34.7 per cent) were single and 40 (33.9 per cent) were male, while 60 (50.8 per cent) were married and 78 (66.1 per cent) were female. In this series one may conclude that females, especially if married, are more likely to require readmission than are males.

Nationality seems to have no special significance in this county where the population is predominantly American born. No attempt was made to analyze further to determine how many "Americans" were of foreign parentage. American Indian patients were almost invariably sent to federal sanatoria so that only one appears on the list.

TABLE VII

Age

6 to 8 years	1
9 to 11 "	4
12 to 14 "	5
15 to 17 "	5
18 to 20 "	10
21 to 23 "	15
24 to 26 "	20
27 to 29 "	22
30 to 32 "	10
33 to 35 "	6
36 to 38 "	3
39 to 41 "	6
42 to 44 "	6
45 to 47 "	1
48 to 50 "	3
66 to 68 "	1
	118

No patients under six years are admitted to this institution. In table 7, and more especially in chart 1, it is clearly shown that the age period between 18 and 32 years inclusive, comprising 77 patients (65.2 per cent), compares well with mortality statistics for tuberculosis, indicating this period to be the most dangerous for relapse or for conditions requiring readmission.

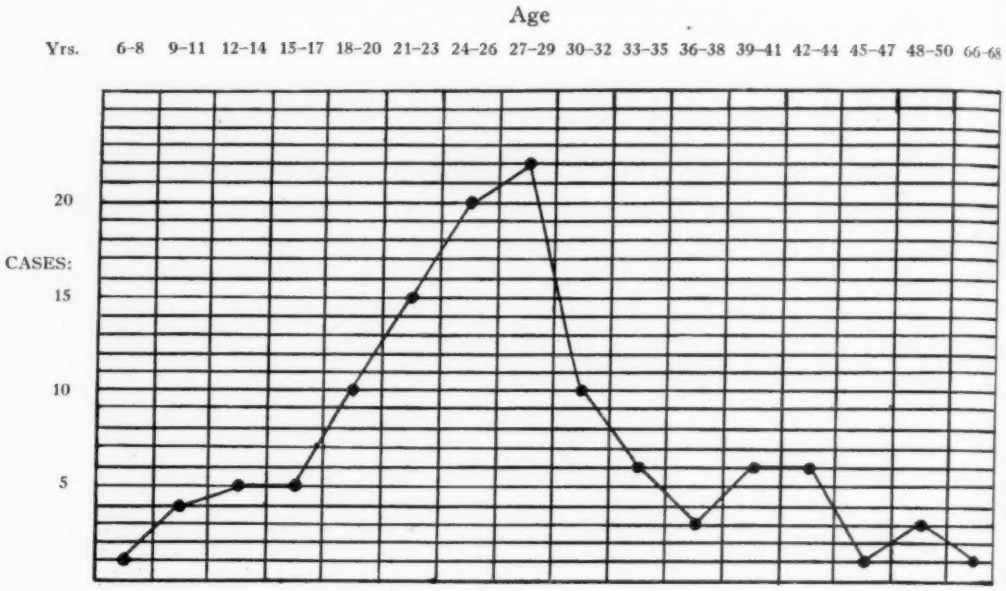
TABLE VIII

Condition on Final Discharge

Quiescent	55
Apparently arrested	7
Active	29
Dead	27
	118

One of the surprising findings is that 29 or 24.5 per cent were discharged as "active." One of the aims of sanatorium care is and should be to discharge the patient at least in the quiescent stage. Of these 29, 24 left against medical advice or by their own request and their treatment obviously had not been completed. In other instances there were active tu-

CHART I



berculous patients outside the institution that urgently required admission. With crowded conditions in the sanatorium, the only possible procedure was to discharge such patients, who, though still "active," were thought capable of maintaining themselves at home, where their home conditions were believed to be satisfactory. In each instance only cases with negative sputum were discharged.

There were 27 deaths (22 per cent) which is a high mortality, but this high rate is not uncommon in public institutions where patients in all stages of tuberculosis must be accepted.

POST-SANATORIUM FOLLOW-UP WORK

At the time of his discharge the patient was given a date to report at the county clinic nearest his home. Emphasis was placed on the importance of keeping the appointment and the necessity of periodic examination and observation until told that he need not report any more. As a general rule the discharged patient was directed to report within a month and thereafter at monthly intervals until a longer period seemed justifiable. Our aim was to follow each patient for at least two years, ordering chest roentgen-ray films at suitable intervals and advising him as to the mode of living consistent with his condition. Table 9 shows these statistics for a period of four years.

One must conclude from the above that, once discharged, a large number of patients (24.2 per cent in this series) disregard advice as to reëxamination or become careless and indifferent. A few can not coöperate because of conditions over which they have no control. The only expense to the

patient was the cost of his transportation to and from the clinic, so financial reasons may be dismissed. Only 10 per cent of our cases continued to report until discharged from further supervision.

TABLE IX

Discharged Sanatorium Patients and Reëxaminations

Period: September 1926 to September 1930 inclusive

Total discharged during period	438
Did not return to clinic for any examination	106 (24.2%)
Returned to clinic for only one examination	35 (8%)
Returned to clinic for 2 to 6 examinations	243 (57.7%)
Returned to clinic until discharged	54 (10%)

The county nurse having so large a territory to cover, was unable to visit the discharged patient as often as could be desired; this might have been a factor, as home supervision can do much to follow up and impress the advice given at the sanatorium.

SUMMARY

1. Statistics are presented from Oakhurst Sanatorium, a small tuberculosis institution owned by Grays Harbor County, Washington State, concerning 118 discharged patients who required readmission once or oftener. The period covers 12 years and 9 months (August 1921 to May 1934 inclusive).

2. The education of the patient concerning tuberculosis in general, the status of his own infection and the particular care he requires is described as a routine measure in this institution. Every possible effort is made to see that he understands his condition and the proper mode of living before discharge.

3. The statistics concern: length of stay in the sanatorium before discharge and the number of readmissions required; the time out of the institution before readmission; apparent cause requiring readmission; occupation, social condition, nationality, sex and age; condition on final discharge

4. In only 10 per cent of those readmitted did the study seem to indicate that it was their own fault. In 17 per cent poor home environment and in 74.5 per cent unavoidable conditions required readmission.

5. Brief statistics are offered relating to discharged patients and their reëxaminations showing how few will continue to report at the clinics in spite of efforts to get them to do so.

CONCLUSIONS

1. Education of the sanatorium patient concerning tuberculosis and his own particular infection must be emphasized; but it is not sufficient to prevent the necessity of readmission (10 per cent in this series).

2. Too short a stay in the sanatorium is a large factor in requiring readmission. The longer the patient remains in the institution the less likely

is the necessity of his readmission because of reactivation of the disease or tuberculous complications. More beds for convalescent or "exercise cases" should be available in each institution and a longer period of observation should be possible, under fairly strenuous living conditions, before discharge.

3. The married female required readmission more than the single male or female.

4. The age period between 18 and 32 years is that in which most readmissions are necessary. This corresponds with the mortality curve for tuberculosis.

5. Leaving the institution against medical advice accounted for 25 per cent of readmissions. In the remaining cases the cause was considered unavoidable.

6. More adequate follow-up work after discharge is necessary but with financial limitations, especially in the smaller institutions, it is difficult if not impossible to carry out.

The writer acknowledges gratefully the assistance of Miss Evelyn Mason, R. N., who prepared the statistics in this article.

MYASTHENIA GRAVIS *

(SIXTH REPORT)

By WALTER M. BOOTHBY, M.D., F.A.C.P., *Rochester, Minnesota*

IN previous articles on myasthenia gravis [3-6] I described in detail the classical picture of the disease and the results of treatment with glycine and ephedrine. In this paper I shall present some of the other features of the disease,† and will include in the bibliography a few of the more important recent articles on the subject.

As all are aware, the mortality of myasthenia gravis has been considered to be high. Goldstein, in Oppenheim's textbook, reported, without any details, 26 deaths in 38 cases; this is a mortality of approximately 70 per cent. However, Goldstein himself saw only a few of these patients, and the rest of the cases he obtained from available reports in the literature. The patients, therefore, did not have the advantage of treatment by any systematic program which would minimize the severity or the associated complications, especially those of dehydration and inanition, attributable to inability to swallow, as a consequence of involvement of the muscles of deglutition.

In the past three years 65 patients afflicted with myasthenia gravis have been seen at The Mayo Clinic. In all these cases the diagnosis of myasthenia gravis was made by consultants of the Division of Medicine and was confirmed by those of the Section on Neurology. Of these 65 patients, 13 have died. Four of the deaths can be excluded from consideration concerning the effect of treatment, because one patient committed suicide, two abandoned treatment, and one died within 48 hours of coming under observation. Fifteen of the patients are now able to carry on practically full time work and are entirely self-supporting. Twenty-five are able to do part time or light work, while only five are at present limited to a life in bed or in a chair. The remaining 12 are able to be up and about their homes and to do varying amounts of small chores.

In spite of unsatisfactory information as to the mortality among untreated patients who have myasthenia gravis, and in spite of the well known frequency of major remissions in the severity of this disease, I am confident that the mortality has been greatly reduced and that the number of patients who can be maintained at either full, or part time, work has been increased. A very severe and serious disease, of long duration, remains to be contended with, one in which many problems remain to be solved. Before there can be ground for reasonable hope of further material improvement in treatment

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From the Section on Clinical Metabolism, The Mayo Clinic, Rochester, Minnesota.

† Motion pictures were shown after reading of the paper to illustrate the characteristic fatigability and effect of treatment thereon.

of the disease, investigators must either know, or at least have a very probable idea, not only of its metabolic disturbances but also of its etiology.

In my laboratory, we have been interested in the first of these two problems, and have been investigating the metabolic abnormalities of the disease. In conjunction with Dr. Adams and Dr. Power we have found that in the acute stage of the disease there is a definite, negative nitrogen balance, a melting away, as you might call it, of body protein, presumably in part muscle protein. On the other hand, after the acute stage is passed there is no longer a negative nitrogen balance, and of course among those patients who are rapidly gaining in weight and strength, subsequent to their reduced stage, following the acute period, there must be a corresponding re-accumulation of protein reserve. On the other hand, marked creatinuria was observed in only six of 28 cases of myasthenia gravis, and in 22 cases the amount of creatine nitrogen excreted was less than 0.04 gm. daily, and many of the patients in the latter group excreted only questionable traces of creatine. The administration of glycine always produced an increase in creatinuria, if it was previously present, and caused a small amount of creatine to appear if it were previously absent. However, a similar reaction was found to occur among normal or practically normal individuals following administration of glycine; therefore, the development of creatinuria following administration of glycine is not limited to any one disease. In fact, the largest increases attributable to glycine were found in cases of progressive muscular dystrophy, in which as is well known, a large percentage of the total creatinine nitrogen is excreted as creatine nitrogen.

In our attempt to find out whether or not the beneficial effects of glycine in decreasing the fatigability of patients who have myasthenia gravis, which we were able to demonstrate repeatedly, was specific for this disease, we administered glycine to a large number of control subjects, some of whom complained of slight or moderate fatigability, such as is so often exemplified by patients who are frequently classified (for lack of a better diagnosis) as being affected with chronic exhaustion. Many of these control subjects likewise experienced a definite decrease in fatigability, and we were therefore forced to conclude that the action of glycine was not specific for the fatigability of myasthenia gravis but had a more general favorable effect on a larger group of cases of nonspecific fatigability. There was, however, one important difference in the action of glycine on the patients who were troubled with the fatigability associated with simple chronic exhaustion from that which it had on patients who had the profound fatigability of myasthenia gravis; the former required only small doses of glycine, often not exceeding 1 gm. or less three times daily, to produce a beneficial effect, whereas most patients who had myasthenia gravis frequently needed 5 gm. three to six times daily. In fact, with few exceptions, none of the control group of subjects could tolerate the large doses of glycine required by patients who had myasthenia gravis, except patients who had progressive muscular dystrophy. The use of glycine in asthenia has a tendency to re-

lieve fatigue, but investigation has not been carried far enough to warrant any definite conclusions as to its range of therapeutic value in the various asthenic states.

The chemical investigations we have pursued in regard to the cause of the beneficial effect of ephedrine in myasthenia gravis, unfortunately have given entirely negative results. Clinically, we have found, however, that large doses of ephedrine frequently can cause harmful effects when continued indefinitely, and that only the small doses of ephedrine of the order of ⅛ grain or even 1/16 grain, three to five times daily, as a rule can be taken with advantage over prolonged periods. We have not yet had an opportunity to investigate the metabolic effects, if any, of the action of physostigmine and prostigmine which Walker has found of immediate but temporary benefit in cases of myasthenia gravis. The reports of Walker, of Pritchard, of Denny-Brown and of Hubble in the " Lancet " indicate that these drugs, especially prostigmine, cause immediate and marked improvement of patients who have myasthenia gravis. However, they point out that these good effects last only a few hours, and that they are then followed by a period of depression. We have confirmed these clinical observations and, like the investigators named, have been unable as yet to find a method of continued administration which will often cause a consistent improvement such as we have found following the use of glycine, both with and without ephedrine.

As regards the etiology of myasthenia gravis, we have coöperated with Dr. Rosenow in attempting to determine whether or not the toxic factor in myasthenia gravis possibly can be of microbic origin. There are phases of the disease which suggest that such may be the case. First, we reviewed the past histories in the available cases and in our third report [4] stated that 35 per cent of our patients (at that time we had had 20 cases) could definitely ascribe the onset of the disease to a more or less severe infection of the upper part of the respiratory tract and the subsequent patients have given similar suggestive evidence. Second, as a result of careful pathologic and histologic studies made by Dr. Robertson, on the material obtained at necropsy of subjects who had had this disease, it appeared possible to him, from the appearance of the microscopic sections of the muscles, that the lymphocytic infiltration and degeneration found might be the result of an infectious process. Dr. Butt, in Robertson's laboratory, has been able to demonstrate streptococci in some of the muscles obtained at necropsy of subjects who had had myasthenia gravis. These studies are still in progress, and we are not yet prepared to do more than state that we consider it advisable to extend them. As such an investigation including the necessary control studies takes time to complete, we have tried clinically, in a few cases, the effect of the use of an autogenous vaccine prepared by Dr. Rosenow from cultures obtained from the throats of patients, because such cultures frequently produce a condition in rabbits and in monkeys that simulates the fatigability seen in cases of myasthenia gravis. While our efforts to determine the etiology of myasthenia gravis are as yet inconclusive, they are

of sufficient interest to encourage us to continue these lines of investigation.

From this brief digression, I must now return to a very practical matter, namely, the early recognition of this disease, in order that the development of its serious manifestations may be prevented, at least in part.

In myasthenia gravis, almost invariably the first muscle groups to show evidence of increased fatigability are the extrinsic muscles of the eyes, which are concerned with focusing, and the fatigability becomes manifest to the patient by transient blurring of the vision and later, actual diplopia. The first symptom usually evident to the patient's family is drooping, or ptosis, of the upper eyelid, especially in the afternoon or evening, after fatigue. In the early stages of the disease these phenomena usually are very transient, and disappear entirely after rest. Somewhat later, or possibly simultaneously, the patient notices that he fatigues easily on talking, especially on strenuous vocalization, as from public speaking or reading. Articulation of long words becomes difficult and as a result the patient's speech sounds thick and indistinct. If, after fatiguing the laryngeal and pharyngeal group of muscles by talking, he attempts to drink liquids or eat solid food, he has serious difficulty in swallowing. Liquid may be regurgitated through the nose; the patient simply has not the strength to masticate solid food, and if he attempts to swallow it he does not succeed and may be thrown into a violent spasm of choking and coughing which, for a few minutes, may be very distressing. After a night's rest the patient is likely to be much better, and the symptoms are apt to recur only toward the end of the day, when the excessive weakness sometimes develops very rapidly. In some cases, after a few weeks of such symptoms, accompanied by a feeling of general lassitude not at that time usually described as actual fatigue, the symptoms may almost entirely disappear for weeks, months, or even years. More frequently, the weakness and lassitude spread to other groups of muscles, and the patient becomes fatigued on the slightest exertion. The muscles especially affected are those of the neck, arms, legs and back. Within six or eight weeks after the onset the patient may be so weak that he can barely turn over in bed or raise his hands to his face; he may have the greatest difficulty in swallowing and, because of fear of choking, may avoid all but the smallest amounts of foods and liquids; these he takes with manifest difficulty. Dehydration and inanition supervene, and subsequently death appears to be rapidly approaching. At this point, a surprising turn in the course of events may develop, even without treatment, and the strength of the patient gradually returns so that in a few weeks he is up and about, although very rarely in untreated cases is he sufficiently strong to work. These cycles of increased fatigability followed by improvement succeed one another at different intervals, although many patients seem prone to have a space of three or four weeks between the lower depths of depression and the higher peaks of remission; in addition, major trends are often superimposed on these minor fluctuations of shorter or longer duration. These long swings and sharp, small, daily, and more pronounced

weekly, fluctuations apparently are explainable only on the assumption of a similar variation in the intensity of the cause of the disease, as, for instance, if it is assumed that the toxin which causes the muscular fatigability is produced by variations in rate of growth of bacteria, as illustrated in tuberculosis. The disease is, however, afebrile.

One of the most distressing and annoying minor factors one has to contend with in the treatment of patients is the thick, slimy, stringy mucus, secreted apparently by the mucous membrane of the mouth and pharynx, and possibly also by the salivary glands. The amount of the mucus varies greatly from day to day, from week to week, and from month to month; whenever it is present in marked degree, the patient's general condition is usually not as good as at other times; in fact, there is often a very definite correlation between the patient's general condition and the amount of this mucus. At the times when there is much oral mucus the patient is usually unable to swallow much, if anything, and until remission occurs it is necessary to feed him by means of a catheter introduced through the nose into the stomach, to prevent the additional ill effects of dehydration and inanition.

Constipation, on the other hand, is not such a difficult condition to control, although it is a very frequent and annoying complication. Repeated enemas are necessary and strong cathartics should be avoided.

In general, there is no pain of any kind connected with the disease, nor is there any soreness or tenderness of the muscles such as there is in typical myositis. On the other hand, there is characteristic flabbiness of all of the muscles of the body, which is especially noticeable if the patient is of rather obese type. The patient cannot smile or pucker up his lips to whistle. The face is absolutely blank, and when talking to him, the physician has the feeling that the patient is completely indifferent to and even bored by the information that is being given him about his disease. This absentee or blank expression has often caused an erroneous diagnosis of a melancholic type of psychoneurosis or even of a brain tumor, and the misinterpretation of the extreme muscular fatigability as mental apathy and laziness. On the other hand, I have seen a case of myasthenia gravis in which the diagnosis, on detailed analysis, could hardly be questioned, misinterpreted because of the fact that the syndrome of myasthenia gravis was superimposed on a mild hysterical basis which the patient had displayed for years previously. There is, of course, no reason why an hysterical type of individual cannot have myasthenia gravis. Admittedly, under such conditions, distinction between the two sets of symptoms, and their correct interpretation, is very difficult.

Illustrative of the characteristic fatigability in this disease, and of the effect of treatment thereon, is the case of an eastern surgeon who has passed through a very severe attack of myasthenia gravis. Twelve months ago he was unable to turn over in bed, he could not light his own cigarette or even raise his hand to put it in his mouth, and he had to be tube-fed for months. He is now in good condition. He has returned to his surgical practice and is able to perform a good day's work. His future course, to be sure, cannot

be predicted, but these patients who have improved as rapidly and as consistently as this surgeon has, have so far continued to maintain their gain. On the other hand, I do not wish to leave the impression that all cases progress so favorably; at present I have five patients who are improving so slowly that I have difficulty in maintaining my own courage, let alone that of the patients. However, even in these cases it is possible to note a slight but unmistakable improvement if their condition at the present time is compared with that four to six months earlier.

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RECENT STUDIES ON ANTI-HORMONES *

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About a year ago at the Chicago meeting of this Society it was my privilege to report upon a theoretical conception which I had evolved in an endeavor to explain certain results which had been obtained in our studies on pituitary extracts, and with a view to directing further work along specific lines. Tonight it is again my privilege to report to you the results which have been obtained in the McGill Biochemical Laboratories during the past year in the course of studies upon anterior pituitary physiology, but with particular reference to anti-hormones.

The anti-hormone theory as originally proposed was as follows:

For each hormone there may be an opposite or antagonistic principle. This antagonist is present in the normal subject but may not be detected until it exceeds in amount the hormone substances with which it is balanced. The analogy was drawn between the hormone anti-hormone complex and a chemical "buffer" system, and in this way the anti-hormone theory was related to the principle of inverse response. The postulated dual hormone control of peripheral structures is analogous to the proved dual nerve control (sympathetic and parasympathetic).

The so-called anti-hormone was considered as a true hormone in every way and not as the result of an antigen-antibody response.

Before discussing this theory in the light of the results of further experimental work, I should like to refer briefly to terminology.

The term "hormone" was originally applied by Starling [1] to stimulating principles such as that contained in the duodenum after treatment with acids and the expression was later extended to include the active principles of all internal secretions. So long as only exciting agents were known there could be no objection to the extension of this term, but since agents which produce depression or cessation of function were known to exist in the body, Schäfer [2] coined the word "chalone" to distinguish such agents which act as depressants or inhibitors from those which were excitant (hormones). A chalone was defined by Schäfer as an endocrine product which inhibits or diminishes activity as distinguished from a hormone, which excites to increased activity. All internal secretions were spoken of by Schäfer as "autacoids." Excitatory autacoids were the hormones and inhibiting autacoids were the chalones. In spite of the very logical nature of Schäfer's objection to the use of the word "hormone" to describe all of the internal secretions, both excitatory and inhibitory, the term has been accepted by general usage.

* Read at the Philadelphia meeting of the American College of Physicians, April 30, 1935.

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While there may appear at first sight to be an analogy between the substances which I have called "anti-hormones" and the "chalones" of Schäfer, the theoretical conception of the mechanism of production and the physiological significance of the former were such as to demand the use of a descriptive and distinguishing term.

The idea of the production of a hormone-inhibitory substance which circulates in the blood stream and is able to neutralize the effects of a hormone was probably first expressed by Möbius.[3] In experiments on thyroidectomized sheep he found that the blood of such animals neutralizes the action of thyroid hormone. Preparations of the blood of such thyroidectomized animals have been made available by the Merck factory under the name of "Antithyreoidin Möbius." This preparation has been used clinically and several authors claim to have obtained good results in cases of Graves' disease. The first investigator who tried to obtain a hormone-neutralizing substance using an endocrine preparation as an "antigen" was probably Blum. Later he repeated Möbius' experiments and confirmed the findings on thyroidectomized animals, but at the same time he noted that thyroid hormone inhibitory substances are also present in the blood of normal sheep. The name "catechin" has been given to these inhibitory substances.[4] Blum's experiments were later extended by Legiardi-Laura, who treated horses with posterior pituitary preparations and found that the serum of such animals decreased the glycosuria in many cases of diabetes.[5] He claimed also that this serum was equally effective in the treatment of hypertension.[6] The experiments of this author and of Blum are difficult to evaluate, since little is said in their original publications about the nature of the antigen used, the doses given, or other details concerning the treatment of the donor animal. The experiments of Koyano [7] in 1923 are open to the same criticism. He injected beef pituitary emulsions intraperitoneally into male rabbits, and stated that the serum of such animals produces marked histological changes in the hypophysis of rats. He called his preparation a "specific immune serum." In 1924 Cotte [8] published a series of experiments in which extracts of fowl ovaries were chronically injected into male rabbits. Thus a "serum anti-ovaire" was obtained. This serum changed the color of the plumage in hen-feathered cocks. The experiment was interpreted as a further proof of Morgan's theory concerning the "corpus luteum cell nature" of certain cells in the testes of the hen-feathered cock. In the same year de Jongh [9] observed that certain insulin preparations are less active in larger doses than in smaller ones, while very large amounts of the same preparation again show an increase in potency. Mathematical considerations led the author to interpret this double-peaked curve as the result of an insulin-inhibitory substance superimposed on the usual insulin effect. The name "anti-insulin" has been coined for this substance. Further purification removed this anti-insulin from the original preparation. Similar experiments led Nobel and Priesel [10] to the assumption that anti-insulin is present in crude pancreatic extracts. Meyer-Bisch and his coworkers [11]

observed that pancreatic secretion increases the blood sugar of experimental animals, and concluded that anti-insulin is excreted into the duodenum. The primary hyperglycemia observed after the administration of crude insulin preparations has also been attributed to the presence of anti-insulin (Wichels and Lauber [12]). Sahyun and Blatherwick [13] observed that rabbits on a high carbohydrate diet, injected chronically with insulin, become "immune" to this hormone, so that even 70 to 100 units do not elicit convulsions. The blood sugar response in such "immunized" animals is also much less than in the non-pretreated controls. The name "anti-hormone" has also been used by Wiese.[14] This author found that testicular extract coagulates the follicular fluid of nymphomanic cows, but has no effect on the follicular fluid of normal animals. This phenomenon was attributed to the formation of "anti-hormones" in the nymphomanic cow. The administration of testis extracts was found to be effective in increasing ovarian activity in cattle, and the author believed this to be due to the production of "anti-hormones."

The earlier experiments of Blum on "catechin" have aroused particular interest because of the good clinical results which many investigators were able to obtain with these preparations. Numerous publications have appeared more recently on similar anti-thyroid hormone preparations. Thus Herzfeld and Frieder [15] have prepared a catechin from blood, and this preparation is now on the market under the name of "Thyronorman." It is said to alleviate the symptoms of Graves' disease. It is interesting to note in this connection that Branovacky [16] showed that the blood of patients suffering from Graves' disease increases the oxygen sensitivity of rats in the well-known Ascher experiment, and that this effect is neutralized by the administration of blood serum from myxedema patients. Asimoff [17] reports that the serum of thyroidectomized sheep inhibits the metamorphosis effect of thyroid hormone in the axolotl; and Gürber and Geszner [18] found that this metamorphosis-antagonizing principle is in the euglobulin fraction. Since Lewit and his coworkers [19] were able to obtain similar effects with normal blood, they doubt the specific nature of such catechins. Recently, Saegesser [20] observed that the serum of myxedema patients neutralizes thyroxin in Reid-Hunt's acetonitril test—a finding which reminds one of Branovacky's experiments concerning the decrease in oxygen sensitivity which we discussed above. Saegesser states that his anti-thyroid substance is lipoid-soluble, and since he also observed that cholesterol exerts a similar effect he considers it possible that this action is a simple chemical antagonism.

This discussion on the historical development of our ideas on the production of hormone-antagonizing substances would not be complete without mentioning that thyro-globulin-antagonizing substances have been obtained by the administration of thyroglobulin,[21, 22, 23] and that specific anti-ferments have been produced and demonstrated in the blood of experimental animals chronically treated with extracts of endocrine glands by Abderhalden, who called such ferments "Abwehrfermente."

The hormone-antihormone theory was proposed: (1) as a possible ex-

planation of certain experimental results obtained in our laboratory; (2) and more important, as a guide to further work. Whether this theory is representative of an actual physiological mechanism will appear with the passage of time, and in the light of the results of the further work. Since this theory was put forward, a year has passed. Such a period is not long, but intensive work done in this field both by my collaborators at McGill and independent workers in other laboratories has strengthened my belief in the reasonableness and the validity of the theory as a sound working hypothesis.

Our own work has shown that specific antagonistic substances (anti-hormones) for the thyreotropic, ketogenic and maturity principles of the anterior pituitary can be demonstrated in the blood of animals treated with extracts containing these principles, and that similar specific antagonistic substances may occur spontaneously in the blood of certain patients.* A specific antagonistic substance for the anterior pituitary-like hormone of human placenta and pregnancy urine has also been demonstrated.

Although Loeb [24] has been unable to obtain evidence of an inhibitory substance for the thyroid-stimulating principle in guinea pigs treated with this principle until they had become resistant to it, others [25, 26, 27, 28] have confirmed our results relative to the demonstration of inhibitory principles in the blood of animals treated for long periods with certain hormone preparations.

Rogowitch [29] noted enlargement of the pituitary of dogs and rabbits following thyroidectomy. Since that time as a result of the pioneer work of Adler,[30] Allen,[31] Smith and Smith,[32] and Spaul [33] on tadpoles; of Uhlenhuth and Schwartzbach [34] on salamander larvae; of P. E. Smith,[35] and Foster and Smith [36] on rats; and of Loeb [37] and Aron [38] on guinea pigs, the interrelationship between the anterior pituitary and the thyroid has been thoroughly established. It is of interest to note here that Loeb was the first to produce hyperplasia in the thyroid of the guinea pig and to point out the possible etiological significance of the anterior lobe principle in Graves' disease. Thyroid hyperplasia has been produced in a variety of animals by treatment with anterior pituitary extracts and a number of investigators have commented upon the lack of response in animals that have been treated for varying periods of time. It was this induced state of resistance to the thyreotropic hormone that Dr. Anderson and I [39] made a subject of special study last year and the outcome of this work was the clear-cut demonstration that the blood of the hormone resistant animal contained a substance antagonistic to the thyreotropic hormone. The method which we have used for the detection of the anti-thyreotropic principle is as follows:

Otherwise untreated hypophysectomized animals are injected twice daily with 0.5 c.c. to 1 c.c. of the serum to be tested. On the second day injections of a standardized thyreotropic extract are started, twice daily. Control animals are treated similarly except that normal serum is used. Metabolic

* I am greatly indebted to Drs. A. D. Campbell and J. S. L. Browne for their co-operation in the selection of blood samples from patients for anti-hormone investigations.

rates are taken daily. In the case of a positive test complete or nearly complete inhibition of the increase in metabolism seen in the control animals is obtained. The test is quite applicable to the study of sera of patients and already we have demonstrated the antagonistic substance in the blood of 10 patients, in all of whom it has occurred spontaneously and not as a result of pituitary therapy. We have of course, obtained numerous negative results with normal human sera.

In general it may be said that wherever we have a specific biological test for a hormone, the same method is applicable with but slight modifications for testing for antagonistic substances. One must be able, of course, to distinguish between specific inhibitory or antagonistic substances and non-specific inhibitory effects. Thus in the case of insulin the existence of a specific anti-hormone substance in the sense to which I have referred has not been established. Mr. Black [40] of my laboratory has been able to show, however, that the hypoglycemic reaction to insulin which has been mixed with normal or diabetic serum and incubated for one hour was greatly lessened when the mixture was injected subcutaneously, whereas the same material given intravenously showed no appreciable loss in potency. Similarly, Dr. Kutz has shown that rats on a high carbohydrate diet may be given increasing doses of insulin daily until 200 units a day are being administered without any hypoglycemic reaction being obtained. This suggested a tolerance to insulin had been developed, but it was shown at once that control rats on the same diet were apparently unaffected by 200 units of insulin. Again, in the case of the parathyroid hormone, Dr. Pugsley has shown that there is non-specific inhibition of the acute effects of the hormone when it is mixed with blood serum and the mixture administered to rats in the usual manner by intraperitoneal injection. No such inhibitory action of serum on the parathyroid hormone was noted when the mixture was given by intravenous injection to the dog. Neither was there any inhibitory effect when serum and hormone solution were injected separately into rats, even though the serum injections were started some days ahead of the hormone.

We feel that the most satisfactory, although not the simplest method of demonstrating a specific hormone inhibitory substance is that of pre-treatment of the test animals with the serum or serum extract to be tested. This is followed by simultaneous injections of a standard dose of hormone and serum or serum extract. Consistent inhibition of the hormone effect with the anti-hormone serum when the experiment is adequately controlled would seem to establish definite proof of the existence of the antagonistic substance in the serum tested. Under some circumstances it is possible to shorten the test by mixing *in vitro* the hormone extract and the serum to be tested and then injecting the mixture. This method is safe only when non-specific inhibitory effects of normal serum can be excluded. No doubt a variety of satisfactory methods of studying the hormone anti-hormone relations in blood and serum or even organs will ultimately be evolved, but for the pres-

ent we are making use almost entirely of the "in vivo" method outlined above.

The establishment of a state of resistance to any hormone extract as a result of long-continued injections of the extract is of itself indirect evidence of the existence in excess amounts of an antagonistic substance. Since such a resistant state may theoretically be due to a variety of causes it seems essential, in any case of an apparent hormone resistant state, that it should be shown that the "resistance" is transferable before a true hyper-antihormone condition can be stated to exist.

Anti-A.P.L. It has been shown that continuous injection of A.P.L. leads at first to a great increase in the size of the ovaries but this effect passes off in the course of a few weeks and the ovaries return to normal or even subnormal size in spite of the continued injections of the hormone. The seminal vesicles and prostate of males treated with A.P.L. continuously have been shown to follow a weight curve somewhat similar to that of the ovaries of treated females.[41] In the light of our results with serum of thyreotropic hormone resistant animals, it was not surprising to find that the serum of animals rendered non-responsive to A.P.L., when injected into immature rats, completely inhibited both the estrogenic and ovarian response to this gonadotropic substance.[42] Anti-A.P.L. serum of relatively high titre has been produced in the rabbit, and recently Dr. Carl Bachman [43] has shown that the antagonistic effect of this anti-substance can be demonstrated in the rabbit. Thus an isolated non-pregnant adult female rabbit was injected twice daily for two days with 0.5 c.c. of anti-A.P.L. rabbit serum. Two hundred units of A.P.L. were then administered and inspection 48 hours later showed that there had been complete inhibition of the normal ovarian response to A.P.L. The characteristic effect of A.P.L. upon the testes, seminal vesicles and prostate of immature males has also been completely inhibited by anti-A.P.L. serum.

Anti-A.P.L. serum is of special interest because Dr. Bachman has been able to show that it contains a true antibody for a proteose-like substance which is a contaminant of our preparation. This true antibody can be demonstrated by complement fixation and precipitin reactions. That it is not the anti-hormone is fairly conclusively shown by the fact that the anti-proteose substance may still persist in the blood of a rabbit weeks after the serum has lost its physiological antagonistic effect upon the hormone due to cessation of A.P.L. injections.

Anti-A.P.L. is of interest in another way because it is, as far as we are aware, a foreign hormone to the animals which have been used to produce successfully an antagonistic serum to it.

We have had as yet no direct evidence of the presence of anti-A.P.L. in the pregnant woman. To assume that it is present would seem on a priori grounds reasonable. At this point I cannot resist re-stating the suggestion that the fundamental disturbance in certain toxemic cases may be a hor-

monal imbalance. This might involve not only A.P.L. and anti-A.P.L. but also true pituitary hormones and even members of the estrogenic group.

Some years ago we became interested in considering the toxemias of pregnancy from the standpoint of hormonal imbalance, but we had to abandon any serious attack upon the problem because of the lack of the necessary base lines characterizing the normal. The working out of these alone we saw would require enormous numbers of animals and, more important still, the development of new methods which would allow of more exact assays of the various hormones involved. The recent work of Marrian and his associates,[44] for example, shows that most of the estrin assays of the past may have to be discarded because nearly all of the estrin in fresh pregnancy urine is ether insoluble, and also of very low estrogenic potency when tested on castrates. In other words, estrin is in the native state combined with some as yet unknown substance which alters both its physical and physiological properties. In 1930 I described a method for fractionating human placenta into three types of estrogenic extracts.[41, 45] One of these, an alcohol soluble, ether insoluble fraction was clearly differentiated from estrin as then known and from the gonadotropic substance "A.P.L." The active principle of the extract was characterized not only by its physical but also by its physiological properties. Some of these latter showed relative ineffectiveness on castrates as compared to marked estrogenic activity on immature female rats, resistance to peptic and tryptic digestion and activity orally. Later this same estrogenic substance was demonstrated in pregnancy urine and crystalline trihydroxyestrin was obtained therefrom only after vigorous hydrolysis in an autoclave had rendered the estrin of the ester ether soluble.[45] Marrian's recent work has confirmed and greatly extended the significance of these earlier observations.

The Anti-Maturity Factor of the Anterior Lobe. It has been shown that daily implantation of fresh rat pituitary into female rats leads at first, as in the case of A.P.L., to ovarian enlargement.[42] After some weeks the ovaries decrease in size and although now unresponsive to implants they respond in a normal manner to A.P.L.

Extracts of pig anterior lobe rich in the maturity factor have been administered over a period of weeks to rats. By the method of pretreatment of immature females with serum obtained from maturity extract resistant rats, the presence of an antagonistic substance for the maturity principle in these sera has been clearly demonstrated.

We have been able to demonstrate the presence of the anti-maturity factor in the blood serum of certain patients. The clinical significance of a positive finding of the anti-maturity factor in the blood stream is not yet fully apparent. The treatment of such a case with pituitary sex hormone would obviously be contraindicated.

The Anti-Ketogenic Principle. Hoffmann and Anselmino [46] and Magistris [47] noted an increase in the acetone bodies in the blood after the injection of anterior pituitary extracts. Burn and Ling [48] found that the injection of

an alkaline extract of bovine anterior pituitary lobes greatly increased the acetonuria of female rats kept on a filtered butter diet. Butts, Cutler and Deuel [49] obtained similar results in fasted rats of either sex. Recently Black, Collip and Thomson,[50] using both the Burn and Ling butter diet and the method of fasting of Butts, Cutler and Deuel, extended these findings and made use of these methods to study the effects of long-continued treatment with anterior lobe extracts rich in the ketogenic factor upon the acetonuria of a high fat diet or of fasting. The method of fasting proved so satisfactory in the preliminary experiments that thereafter it was used as a routine. The results obtained in this study were quite clear-cut. The characteristic acetonuria of fasting was practically abolished in those animals which had been made resistant to the extract by repeated injections. Also normal animals pre-treated with serum from resistant animals manifested no appreciable ketonuria when fasted and injected with a standard dose of a ketogenic extract. Mr. Black [51] has shown that the ketogenic hormone resistant animals develop practically no ketosis when given massive doses of phlorhizin, in spite of the fact that the usual glycosuria was produced. The control animals had extreme ketosis and those on the larger doses died. Incidentally, I may remark that we have definite proof that the ketogenic principle is quite separate and distinct from the thyreotropic, adrenotropic and growth hormones.

Dr. Kutz has been able to demonstrate recently that pancreatectomized dogs given suitable dosage for a sufficient time of anterior pituitary extract containing the ketogenic principle, during a period in which they are being maintained in good condition by adequate insulin therapy and dietary control, may on withdrawal of insulin show no appreciable ketonuria. Such animals are in many respects similar to the " Houssay dog "—namely, the hypophysectomized-pancreatectomized animal.

The recent report by Long and Lukens [52] of the failure of adrenalectomized-pancreatectomized cats to show ketosis even when injected with anterior pituitary extracts is of tremendous importance in relation to the physiology of the ketogenic principle, for it suggests that the latter may work as a trophic hormone on the suprarenal. Since our studies have clearly established the fact that the purified adrenotropic principle of the pituitary is non-diabetogenic in the Houssay preparation and non-ketogenic in the fasting rat, it is possible that there are two trophic hormones of the anterior pituitary acting on the suprarenal. On the other hand, Mr. Black of our laboratory has been able to obtain marked ketogenic effects with anterior pituitary extracts not only in hypophysectomized rats, in thyroidectomized rats, in thyroidectomized-hypophysectomized rats, but in adrenalectomized rats. In view of the fact that the rat may have small amounts of accessory cortical tissue, Mr. Black's positive results on adrenalectomized rats treated with ketogenic extract are not necessarily in contradiction with the negative results of Long and Lukens on the adrenalectomized cat.

Our conception of the mechanism by which the ketogenic principle

functions must of necessity remain rather vague until the results of further work enlighten us. It is, however, of great interest to note that we have evidence of the occurrence spontaneously in the blood of several patients of an anti-ketogenic principle and very recently Dr. Kutz has been able to demonstrate such an anti-ketogenic substance in extracts of certain urines.

The Anti-Growth Factor. We have abundant indirect evidence of an anti-growth factor. Hypophysectomized rats treated with purified growth hormone almost invariably cease to respond to it after a period of five to six weeks. Serum from such animals has antagonized the growth hormone in otherwise untreated hypophysectomized rats. Unfortunately our experiments of this type have been limited in number and a much larger series will have to be carried out before direct proof of an anti-growth principle can be said to have been definitely established. Animals treated with crude anterior lobe extracts have continued to grow for longer periods and the very interesting possibility arises that the production of anti-hormones may be greatly modified by the degree of purity of the hormone extract used in treating the experimental animals.

Discussion

The experimental evidence which I have given furnishes strong support for the anti-hormone theory. I do not state that other interpretations may not be made of the results. All of the various extracts which we have used to demonstrate the production of antagonistic substance contain protein-like material, so that there was always the possibility of a true antigen-antibody response in the treated individual. We do not believe that this latter possibility affords an adequate explanation for the anti-hormone responses observed, for the following reasons:

1. The studies of Dr. Carl Bachman on anti-A.P.L. serum have shown that the anti-hormone effect does not parallel the anti-body content.

2. Rats have been made resistant to the maturity hormone of rat pituitary by continued implantations of rat pituitary.

3. Rats made resistant to the ketogenic principle by a long period of daily injections of an extract made from ox anterior lobes have been shown by Mr. Peter Black to be equally resistant to the ketogenic extract made from sheep or pig anterior lobes.

4. There is spontaneous occurrence in the serum of certain individuals of a substance capable of inhibiting an anterior lobe principle. Thus positive inhibition of the maturity principle, of the thyreotropic principle, and of the ketogenic principle has been observed.

Site of Production of Anti-Hormones. We are completely without direct evidence which might throw some light on the source of the antagonistic substances produced in animals treated over a long period with anterior pituitary principles. Anderson and Collip [53] demonstrated the development of a refractory state to thyreotropic hormone in hypophysectomized rats.

The anti-thyreotropic substance was demonstrated in a thyroidectomized dog after several weeks of treatment with the hormone. Castrated rats and rabbits have been successfully used to produce anti-A.P.L. sera. It would therefore appear that the target organ can be excluded as playing an essential rôle in the production of the antagonistic hormone.

On the other hand, there is some evidence that antagonistic principles may occur in the same gland. Riddle [54] has recently shown that purified prolactin is definitely antagonistic to the gonad; and we find that prolactin has a definite inhibitory effect on the action in the rat of a maturity hormone extract. Whether antagonistic effects of this type are of the same order as the anti-hormone effects cannot be stated.

In view of the fact that a somewhat extensive search for evidence of the existence of anti-hormones to estrin, to parathyroid hormone and to insulin has failed as yet to demonstrate such, it is possible that the anti-hormone theory should be applied only to trophic principles.

It must be borne in mind also that a resistant state to a certain hormone may be due to a purely local condition and not necessarily to the presence in abnormal amounts of an anti-hormone or a specific antagonistic substance. Thus it is now well established that the ovaries of the very young animal are non-responsive to anterior lobe maturity hormone. Certain hypoglandular as well as hyperglandular, states may be due to decreased or increased responsiveness respectively of the gland concerned to the specific trophic principle normally influencing it.

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EXPERIMENTAL AIR EMBOLISM *

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The literature contains many case reports and a number of experimental studies of air embolism; but opinions still differ widely regarding its clinical significance and its mechanism.

Hobart Hare, in 1902, injected 60 c.c. of air into the jugular vein of a dog without the production of any symptoms whatever. In two patients, 2 to 3 c.c. of air were injected into the median basilic vein without ill effects. W. H. Luckett, in 1913, reported a case of air embolism in the lateral ventricles of the brain following a fracture of the skull in which the air was probably forced into the ventricles, during an attack of sneezing, through a fracture in the frontal sinus. Death occurred 21 days after this accident, and necropsy proved the presence of air in the ventricles.

Edward von Adelung cites the instance of a man with pulmonary tuberculosis and pleural adhesions who, while undergoing an artificial pneumothorax, developed paralysis of the right arm and leg, cyanosis, cardiovascular shock, and unconsciousness. He completely recovered the next day. There have been a number of similar reports of air embolism following artificial pneumothorax.

Charles Pierre Mathé reported a case of fatal embolus due to inflation of the bladder with air. Here the formation of emboli took place, he claimed, by the entrance of air into the venous circulation, either through an ulceration of the mucosa caused by some preëxisting pathological lesion such as ulcer, tumor, or laceration or as a result of injury to the mucosa from over-distention of the bladder. Death occurred as soon as the patient became convulsed and cyanotic.

Ewald and Kobert conclude after experimentation, that air may traverse the intact lung tissue and escape into the blood vessels or pleural cavity when intrapulmonary pressure is greatly increased.

The occurrence of air embolism of the retinal vessels of man and rabbits was described by Hans Barkan in 1928. The retinal arteries became completely filled with air and the entire fundus contained innumerable fine glittering lines. These hung together like spider webs and formed an extraordinarily fine network over the whole fundus. This condition has been observed in man following puncture of the maxillary antrum, and as a result of intracranial or neck surgery.

An interesting report of air embolism occurring during pneumarthrosis of the knee joint is given by Samuel Kleinberg. He injected oxygen at low pressure into the knee joint. The injection lasted only half a minute when suddenly the patient became pulseless. The pupils dilated widely and un-

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consciousness ensued. With improvement of circulation, resulting from the administration of stimulants, the patient became wildly delirious, requiring the strength of several attendants to hold him. Within a few days he completely regained consciousness and his further recovery was uneventful.

Allen and Clark conclude that simple thoracentesis may produce a bronchovenous fistula which will serve as a portal of entry for air into the pulmonary veins. They claim that experimental work on dogs demonstrated gravity as a determining factor in the distribution of air; when the head was elevated, the head, neck and forelegs received air; when the head was depressed, the trunk and hind legs received the air and the coronaries were heavily involved. The air tended to float on the blood and to seek the upper parts of the body. Even where the stream is rapid and violently churned, as in the heart and aorta, air and blood fail to mix thoroughly. Air may remain stationary in the bend of a vessel or, should gravity dictate, it may even pass in the direction opposite to that of the blood.

The literature reveals three schools of thought regarding the causation of death from air embolism. The first accepts a cerebral death; the second a respiratory death, with suffocation ensuing from obstruction of the pulmonary artery; and the third, a cardiac death. The last is thought to be caused by a lowering of intracardiac pressure and circulatory failure.

The purpose of our investigation is merely to show the course pursued by air, when injected into a peripheral vein, and its effects.

Protocol

Experiment A. A daily injection of 0.5 c.c. of air was administered to rabbits, weighing approximately 2.5 kilo., for five days without any untoward effects. This was gradually increased. When 2 c.c. (average) were administered at one time, the rabbits developed convulsions and died within three minutes. As long as less than 2 c.c. (average) was administered, and sufficient time allowed between injections, the rabbits recovered.

Experiment B. Five c.c. of air were given to a dog weighing 15 kilo., as rapidly as one could inject it into the femoral vein, without any untoward results. The dose was doubled every day until 50 c.c. were reached and still there were no ill effects. As we increased the amount to 75 c.c. the animal became dyspneic, listless and the mucous membrane showed a cyanotic hue. But, in about five minutes, the dog made a complete recovery. The air dose was administered again daily for one week. Similar experiments were carried out on a few other animals. When the dose was doubled to 150 c.c. the animals became extremely ill, markedly cyanotic and dyspneic with a marked pulling of the intercostal muscles, but after 15 minutes they recovered. It was only after the amount was increased to 250 c.c. that the animal died. These experiments were repeated with similar results.

Experiment C. In an average sized dog, we have cut the veins of the neck, laid them open and yet by pressing and relaxing the thorax (the

method used in artificial respiration) we have been unable to introduce air into the circulation. A small amount of air could be felt passing along the vein for about a quarter of an inch if a funnel attached to a cannula was raised about two feet above the neck of the animal. There were no untoward effects and upon removal of the cannula blood again appeared at the proximal end of the vein.

Experiment D. An overdose of morphine and chloretone was given to some animals after small amounts of air had been injected (1 c.c. to rabbits and 20 c.c. to dogs). The large vessels were ligated wherever possible and the organs then sectioned under water. The only place where air was consistently found was in the pulmonary artery and its branches. In those animals where the amount of air given was above the lethal dose, the air was found in the right ventricle, the coronary veins, right auricle and even in the superior and inferior vena cava if the amount injected were large enough. At no time, however, did we find air on the left side of the heart or in any other organ.

Conclusions

1. The amount of air necessary to produce death when injected intravenously differs with each animal (rabbits and dogs) and seems to be directly proportional to the size of the pulmonary artery and its branches. The lethal dose for a rabbit is approximately 0.5 c.c. per kilo., while in a dog it is 15 c.c. per kilo.

2. The injected air is found in the pulmonary artery and its branches. Only if the volume of air injected is in excess of the volume of the pulmonary artery and its branches, will it be found in the right ventricle, right auricle and in the superior and inferior vena cava. No air could be found in the left side of the heart or in any of the other organs after sectioning them under water. The air, when introduced intravenously, did not go against the blood stream in spite of variations in gravity.

3. The effect of the air is that of a circulatory tampon blocking the pulmonary circulation.

4. We were rather surprised that the speed of injection was of little importance. No matter how slowly it was injected, the air accumulated in the pulmonary artery and its branches. As long as the injection period was shorter than the absorption period, the result was about the same.

5. If a large volume of air is accidentally injected intravenously—judging from the signs seen in animals—the following may be looked for: shock, dyspnea, cyanosis, slow pulse, convulsions and death.

6. In cases where a large volume of air is accidentally injected it would be logical to aspirate the right ventricle since it is easily accessible.

7. The amount of air which may be accidentally introduced in humans during an ordinary intravenous injection should occasion no clinical manifestations.

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RECENT ADVANCES IN CARBOHYDRATE METABOLISM WITH PARTICULAR REFERENCE TO DIABETES MELLITUS *

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Since the discovery of von Mering and Minkowski some 46 years ago, that total extirpation of the pancreas in animals produced a condition indistinguishable from diabetes mellitus in man, three major problems have confronted both physiologists and clinicians interested in this disease. They are: 1. The isolation and clinical application of the internal secretion of the pancreas. 2. The mode of action of this pancreatic hormone. 3. The elucidation of the mechanisms involved in the production of the diabetic syndrome.

The first problem was solved in 1922 when Banting and Best succeeded in preparing insulin. This discovery was at once followed by the world-wide use of this substance in clinical diabetes with the happy results that we are all familiar with today.

In spite of the enormous volume of work upon the subject the mechanism of insulin action is at present but ill defined. It would appear to be fairly well established that insulin has a dual action leading to increased tissue (chiefly muscle) utilization of glucose and to a decreased formation in the liver of glucose from non-carbohydrate sources.

The essential problem still remains unsolved. Briefly this is, what alterations are produced by insulin in the glucose molecule that enable it to be so easily metabolized? Several workers have attempted to show that in the presence of insulin glucose is converted into an active form readily utilizable by the cell. None of these attempts have been successful and at the present time we must admit our inability to explain this fundamental property of insulin.

It is in the elucidation of the third problem that considerable headway has been made in recent years. This problem is: "What mechanisms are involved in the production of the diabetic syndrome which occurs following total pancreatectomy in animals or as a result of disease in man?" The sequence of events in either of the above cases is as follows: (*a*) marked hyperglycemia and glycosuria which persist during fasting, (*b*) increased protein breakdown and conversion to glucose, as is indicated by the high nitrogen excretion and the constancy of the urinary glucose-nitrogen ratio, (*c*) the appearance of large amounts of aceto-acetic and beta-hydroxybutyric acid in the urine, (*d*) the quantitative excretion of ingested carbohydrate along with the failure of the respiratory quotient to rise above the level

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indicating fat oxidation when such carbohydrate is given, (*c*) the development of severe acidosis, coma and finally death.

Two theories have been advanced to explain the above series of events. The first of these may be termed "the failure to utilize glucose." The proponents of this idea hold that in the absence of insulin there exists an almost complete inability of the cells to oxidize glucose. This deprivation of carbohydrate in turn throws the burden of supporting the metabolism upon protein and fat. The increased utilization of protein accounts for the high urinary nitrogen and the constant glucose-nitrogen ratio in the urine, since a constant proportion of protein is assumed to be converted into glucose. The increased amounts of fatty acids that are mobilized are broken down in the usual manner as far as aceto-acetic and beta-hydroxybutyric acids. The further metabolism of these substances to CO_2 and water is, however, held to be dependent upon the oxidation of a certain proportion of glucose. From this assumption has arisen the aphorism that the fats burn in the flame of the carbohydrates. From a biochemical point of view this relationship has been spoken of as the ketogenic-antiketogenic ratio, or the fattyacid—glucose ratio. Since, as we have seen, a virtual absence of glucose oxidation is held by this school to be the essential defect, it is obvious that if the ketogenic-antiketogenic ratio is a biological rule, then these ketone bodies must accumulate to a marked degree in diabetes, since there is not only a failure to metabolize them but also an increased production of them as the fat stores of the body are drawn upon in increased amounts. As a result they accumulate in the blood and tissues and are a contributory factor in the development of the acidosis and coma.

In 1901 the discovery of Blum [1] that the injection of epinephrine was followed by hyperglycemia and glycosuria gave rise to the theory that this substance was the physiological antagonist of the internal secretion of the pancreas. The Vienna School headed by Von Noorden, Falta, and others built up an elaborate theory of glandular interrelationships between the thyroid, adrenal medulla and the pancreas to explain the effects of pancreatectomy. This view has come to be known as the "over-production theory." In brief, their main arguments were that the diabetic condition is not entirely brought about by a failure to metabolize glucose, but rather by an over-production of this substance from protein and fat. Furthermore, using the glycosuric action of epinephrine as their argument, they indicated that the uncompensated action of the adrenal medulla in the absence of the pancreas brought about this over-production. In brief, diabetes mellitus was in reality hyperadrenalism.

The collective work of many investigators has exposed the falseness of this view. In the first place, epinephrine, although producing glycosuria and depletion of liver glycogen, does not stimulate protein metabolism nor will it produce the degree of ketonuria observed in diabetes. Nor does its continued injection produce a persistent glycosuria such as is seen even in the fasting diabetic animal. More recent work of the Coris [2] has demon-

strated that epinephrine, although at first reducing liver glycogen, finally brings about a marked increase in this substance at the expense of the muscle glycogen. It would appear at the present time that the effects of epinephrine are limited to the formed carbohydrate elements in the body and that it is incapable of stimulating gluconeogenesis from protein, which after all is the most characteristic metabolic disturbance in diabetes mellitus.

Until recent years the theory that the essential factor in the causation of the diabetic condition is a failure to oxidize glucose has been accepted by the majority of competent workers in this field. All the experimental evidence favored this view while the work advanced by the supporters of the pluri-glandular hypothesis has in general either been poorly conceived or else capable of satisfactory explanation in the terms of the opposing view.

The differences between these two schools are not confined to those concerning diabetes alone. As mentioned above, the over-production theory contends that the conversion of fatty acids to glucose is one of the factors creating the excessive sugar production in diabetes. It is a logical assumption that this transformation of foodstuffs is a normal phenomenon and that the absence of insulin allows this conversion to proceed in an unchecked and exaggerated manner. This is not yet generally accepted, and, in fact, there is no experimental evidence to support such a view. It is, however, agreed that there is excessive production of glucose from protein, but the first school looks upon this as a consequence of failure of glucose oxidation, while the second holds it is a primary feature of the diabetic state induced by the uncontrolled action of the contra-insulin hormones. The failure to ascribe to epinephrine this antagonistic rôle and the absence of evidence as to any other substance acting in this manner placed the over-production theory in a precarious position.

This sharp difference of opinion has to some extent been cleared up by the work of recent years. Thus it had long been noted in acromegaly, which is associated with tumors of the anterior pituitary, that glycosuria and diabetes were exceedingly frequent complications. Furthermore, since the discovery of insulin, the observation was made that hypophysectomized animals were exceedingly sensitive to this hormone, indicating that some normally antagonistic action to its injection was absent.

About 1927 Houssay and his associates [3] began the publication of a long series of papers concerning the effect of previous hypophysectomy upon the diabetes following total extirpation of the pancreas. This work, for the light it has already thrown upon the diabetic state and the possibilities it has opened for future knowledge of this condition, entitles it to be ranked with that of Minkowski, and Banting and Best as a milestone in our knowledge of this disease.

Houssay's first experiments were carried out upon toads. They were, however, rapidly extended to dogs. The findings in both species were as follows: 1. After pancreatectomy in an hypophysectomized animal the degree of hyperglycemia and glycosuria was much diminished compared to

that following pancreatectomy in an intact animal. 2. The nitrogen excretion and the dextrose-nitrogen ratio in the urine were also decreased. 3. Ketonuria was markedly reduced and diabetic acidosis and coma did not occur. 4. As a consequence of these changes the animals survived for a long period. The diabetes was not entirely obliterated, but was transformed from a rapidly fatal condition into one of mild degree. Thus dogs which ordinarily live only about two weeks after pancreatectomy survived for six months or more if the hypophysis was also removed. 5. These doubly operated animals were extremely liable to hypoglycemic episodes especially if fasted, glucose injections being often necessary to save their lives. 6. The carbohydrate tolerance, although not normal, was often greatly superior to that of the control depancreatized group. 7. Marked loss of weight occurred in all the doubly operated animals that survived for long periods, and in fact these animals ultimately succumb to inanition. This loss of weight is in part to be attributed to the absence of the external pancreatic secretion and partly to the mild diabetic state that persists.

In the first experiments upon toads Houssay [4] was able to show that implantation of the anterior lobe of the pituitary brought about a return of the diabetes to its usual severity. Similar experiments in dogs were at first unsuccessful but in more recent work he [5] has made use of alkaline extracts of bovine anterior pituitaries. With these extracts Houssay was able to exaggerate markedly the diabetic state of his doubly operated dogs. He [6] has also reported that these extracts produce hyperglycemia and glycosuria in normal animals. In this he is supported by Evans,[7] Baumann and Marine [8] and others.

For my own part, up to the present I have not seen highly purified anterior pituitary extracts produce this effect in normal animals, and other workers have reported similar negative results.[9] The production of a persistent diabetes in normal animals by anterior pituitary injections is only one of the many problems that await future investigation.

How are we to explain these findings in the light of the present theories of diabetes? It appears to me that Houssay has conclusively demonstrated the participation of the anterior pituitary hormones in the sequence of events following total pancreatectomy.

Thus, in the absence of these hormones, sugar production from protein is decreased and to judge from the urinary dextrose-nitrogen ratio a greater portion of the glucose formed from protein is utilized. Furthermore, the capacity of the tissues to utilize carbohydrate as judged from the carbohydrate tolerance is increased.

Even more striking is the virtual absence of ketonuria. This would imply that the mobilization of fat is decreased or else that the ketone bodies are being normally metabolized as might be expected if carbohydrate oxidation was resumed.

It will at once be realized that here is the first satisfactory evidence in favor of the pluri-glandular or over-production hypothesis. The anterior

pituitary hormones may well be the long sought contra-insulin hormones. Their action would be expected to drive up sugar production in the liver from protein, and possibly to decrease the capacity of the tissues to utilize glucose. Neither of these points is yet settled, but we do know that the injection of these anterior pituitary hormones confers upon the organism marked resistance to the usual effects of insulin. In seeking an explanation of the manner by which these effects are produced it should not be forgotten that hypophysectomy causes marked changes in other organs of the body. Thus there occurs atrophy of the gonads, thyroid and adrenals and probably of the parathyroids and thymus. Now it is already known that alterations, particularly excess of the thyroid secretion, cause disturbances in carbohydrate metabolism. Houssay [3] and his co-workers have shown that thyroidectomy does not influence the course of a total experimental diabetes in dogs. We may therefore dismiss for the present the possibility that it is absence of the thyroid secretion that is responsible for these changes in the diabetes of hypophysectomized animals.

The only other gland whose secretions are known to influence carbohydrate metabolism is the adrenal. This is a double gland consisting of a cortical portion necessary for life and a medulla which is an integral part of the sympathetic nervous system. The medullary secretion is epinephrine and we have already narrated the failures to confer diabetogenic properties upon this substance. However, when we examine the adrenals of hypophysectomized animals the remarkable fact is found that the atrophy is limited to the inner layers of the cortex, the medulla remaining intact.

The establishment of the effects of hypophysectomy upon diabetes coupled with this atrophy of the adrenal cortex that follows hypophysectomy has stimulated fresh interest in the possible effect of the adrenals upon diabetes. In the past, many experimenters have attempted with indifferent success to prepare animals in which both the adrenals and pancreas had been removed. The short survival of such preparations has precluded any attempts to evaluate the results obtained. It has, however, been abundantly demonstrated that removal of the adrenal medulla alone or suppression of its secretion by section of its nerve supply does not prevent the characteristic sequence of events when the pancreas is subsequently removed.

In spite of this fact, Barnes and his co-workers [10] have recently begun another investigation upon the effects of suppression of epinephrine secretion upon pancreatic diabetes in the dog. They have found that in certain dogs such a procedure produces some amelioration of the diabetes; this effect, however, is inconstant. Of greater interest is their finding [11] that the amounts of insulin required to maintain such animals is often only a fifth or a quarter of the amounts required when the adrenal medullae are active. If epinephrine is infused at a physiological rate into such animals the insulin requirement promptly returns to normal.

The work of de Takats and his associates [12] is closely related to that of Barnes. These workers have shown that section of the splanchnic nerves,

celiac ganglionectomy or denervation of the adrenals, results in a decreased insulin requirement both in dogs and in human diabetics. This work is still incomplete and at the present time there is no satisfactory explanation of the results obtained by these workers. In interpreting these experiments it should be remembered that epinephrine does not alter the nitrogen metabolism and there is good reason for believing that its effects are limited to the formed carbohydrate stores of the body. There is no doubt, however, that it acts as an antagonist to insulin so far as these stores are concerned since it is poured into the blood stream in response to an insulin hypoglycemia and causes a prompt discharge of liver glycogen and a consequent increase in blood sugar.

About 16 months ago my associates, Drs. Lukens and Evans, and myself became interested in the rôle of the adrenal cortex in endogenous carbohydrate metabolism. In addition to the marked effect of hypophysectomy upon this organ we were cognizant of the fact that Britton and his associates had advanced the view that the prepotent function of this gland was in the regulation of carbohydrate metabolism. Thus Britton,[13] Zwemer [14] and others have shown that the marked hypoglycemia and low liver glycogen stores of adrenalectomized cats are relieved by injections of cortical extracts that will maintain such animals in good health. It should also be recalled that a low blood sugar level is a common finding in Addison's disease.

In our work we have used cats and have found it possible to remove both adrenals and the pancreas. Such animals have lived in reasonably good health for considerable periods of time (as long as 28 days) and thus the results obtained are not invalidated by the objection that we were dealing with moribund animals. In all our experiments cortical preparations have been injected daily but no insulin was given, since it seemed to us that in studying the effects of these procedures the absence of this hormone is essential if we wished to draw any conclusions as to their effects upon a total diabetes.

The results are of some interest and I hope I may be pardoned for introducing our own work in a review of this kind. In the first place the effect of a total adrenalectomy upon pancreatic diabetes is strikingly similar to that of hypophysectomy. Thus, (1) The hyperglycemia and glycosuria are much reduced. (2) The nitrogen excretion and D/N ratio are decreased. (3) Ketonuria is very slight and acidosis does not develop. (4) The survival of the animals is much increased. The totally depancreatized cat dies in about four days, while the usual length of life of the doubly operated animal in the absence of infection is about 2 to 3 weeks. (5) Hypoglycemic episodes are common. (6) There is occasionally some improvement of carbohydrate tolerance but we have not observed, either in these or in the hypophysectomized-depancreatized cats, such striking improvements as have been reported by Houssay, Barnes and others in the dog. In another series of experiments we have shown that it is the adrenal cortex and not the medulla that is responsible for these changes, since animals from

which the adrenal medulla is removed rapidly die of typical diabetes after pancreatectomy.

While our work was in progress Hartman and Brownell [15] have reported similar findings in cats. One of these animals survived two months.

We next attempted to restore the full diabetic condition by injection of various hormones. It will be recalled that in the hypophysectomized-depancreatized dogs Houssay was able to accomplish this by the injection of crude alkaline extracts of anterior pituitary. In our work we have used the anterior pituitary preparation of Squibb.* This extract in doses of 5 to 10 c.c. causes a marked and often fatal recurrence of ketonuria and acidosis in the hypophysectomized-depancreatized cat. It also slightly increases the glycosuria, but in a degree not at all comparable to that of the ketonuria. Thus nine such cats were injected while in good health; of these, eight showed a marked ketonuria, four dying in coma within 48 hours.

To our surprise, similar or larger injections of this extract into adrenalectomized-depancreatized cats did not affect the ketonuria or glycosuria. Thus eight such animals were injected. Seven did not respond; the eighth animal was found at autopsy to possess an accessory cortical body.

In both groups of animals epinephrine in doses as large as 1.0 mg. a day, although increasing the glycosuria, did not alter the urinary nitrogen or ketone bodies.

The above experiments strongly suggest that the ketogenic activity of anterior pituitary extracts may be mediated through the adrenal cortex. In this respect it will be recalled that the gonad and thyroid stimulating principles of the anterior pituitary are inactive in castrated or thyroidectomized animals.

It would appear that the pituitary extract we were using does not possess very marked glycosuric activity. Evidence has also been advanced from other laboratories that the glycosuric function of such extracts may be due to a principle separate and distinct from that causing ketonuria. It is obvious that further investigation of this possibility will be of great interest.

I think it is probable that both hypophysectomy and removal of the adrenal cortical tissue are altering the response to pancreatectomy by interference with the same metabolic mechanism. At the present time it would appear that in the absence of either of these internal secretions the marked formation of sugar from protein and the accumulation of the intermediary products of fat metabolism which usually follow pancreatectomy are greatly decreased.

Now pancreatectomy is not the only method by which sugar formation from protein can be stimulated. Another method is deprivation of food. During a fast the blood sugar is maintained by this mechanism. It has been observed that neither hypophysectomized nor adrenalectomized animals will withstand fasting. Such animals under these conditions develop hypo-

* We are indebted to Dr. J. J. Durrett of E. R. Squibb & Sons for a generous supply of this extract.

glycemia which may prove fatal unless relieved by glucose. Another way of stimulating gluconeogenesis is by the injection of the glucoside phloridzin. This substance alters the renal permeability to glucose so that large amounts of sugar are lost in the urine. As a consequence sugar formation from protein is greatly increased and large amounts of ketone bodies appear in the urine.

Houssay [16] has shown that in hypophysectomized dogs the injection of phloridzin is followed by an atypical response. These dogs do not form nearly as much sugar from protein and in addition do not develop such a severe ketonuria as do the controls. My associate, Dr. Gerald Evans, has carried out similar experiments upon adrenalectomized rats. He finds that these rats excrete only 40 per cent of the sugar and 18 per cent of the ketones found in the normal control group. Animals in which only adrenal cortical tissue is left behave as do normal rats. Furthermore, Dr. Evans has made the interesting observation that exposure of rats to low oxygen pressures results in a new formation of sugar from protein, as is shown by the greatly increased amounts of liver glycogen and the increased urinary nitrogen excretion found after such an experiment. If only adrenal cortical tissue is left intact the rats still form this new liver glycogen at the expense of protein, but totally adrenalectomized or hypophysectomized animals do not respond in this manner.

We have seen then that four procedures by which sugar formation from protein is increased—to wit, pancreatectomy, fasting, phloridzinization, and exposure to low oxygen tensions—are relatively ineffective in the absence of either the hypophysis or the adrenal cortex. We have suggested that the hypophysis controls this sugar formation from protein through the adrenal cortex. This is tantamount to saying that the adrenal cortex contains a diabetogenic substance or a contra-insulin hormone. The question may then be asked as to why the cortical extracts that we have injected into the animals did not exert a diabetogenic action. There are two possibilities: (*a*) that sufficient extract was not administered to cause a total diabetic response, or (*b*) that these extracts did not contain this, at present, hypothetical factor. If the latter is true the adrenal cortex must contain at least two hormones, one necessary for the maintenance of a proper water and salt metabolism and another concerned with sugar production from protein and possibly other aspects of metabolism.

Much of what I have said in the latter part of this address is not yet firmly established, but I have chosen to discuss it here to justify the title of my address. Surely we are justified in assuming that out of all this recent work upon carbohydrate metabolism there will emerge knowledge of great importance to all who are engaged in the treatment of diabetes mellitus in man. Even at the present time we are confronted with the fact that diabetes mellitus is not necessarily always a disease of the pancreas. We are now entitled to consider that in some cases the defect is to be attributed to the overactivity of other glands of internal secretion.

In a like manner we must now admit that in diabetes mellitus the overproduction of sugar is not necessarily a consequence of failure to oxidize glucose, but that it may be due to the uncontrolled activity of other endocrine glands. This hyperactivity may be the primary cause of the disease or may be the result of an endocrine imbalance induced by a deficient or absent insulin supply.

Finally, it should be emphasized that a normal carbohydrate metabolism is not possible if the insulin supply is deficient. Removal of the contra-insulin hormones ameliorates the destructive conversion of the tissue substances into glucose. It does not reinstate the normal carbohydrate metabolism.

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THE INCIDENCE OF THE CLINICAL TYPES OF SYPHILIS IN MALES, IN PREGNANT AND NON-PREGNANT FEMALES *

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In a series of studies of neurosyphilis we [1] reported the incidence of neurosyphilis in males, nullipara and multipara.† In order to make a comparison of the incidence of neurosyphilis with other types of syphilis in the same groups we have reviewed 800 cases of syphilis as they were admitted to a large venereal disease clinic or were under routine treatment. Our findings are reported in this paper.

In the selection of these cases, patients with early syphilis as well as those with late syphilis, with minor pupillary or reflex changes not diagnostic of neurosyphilis, who had not had an examination of their spinal fluid, were excluded. As was pointed out in the previous paper, the incidence of neurosyphilis is probably higher in this, a venereal disease clinic, than in the average medical clinic where syphilis is frequently discovered incidentally.

The following table indicates the frequency of the various types of syphilis in these three groups:

Table I

Incidence of Various Types of Syphilis in 800 Patients

	Nullipara 219 cases	Multipara * 148 cases	Males 400 cases
Early Syphilis (Early Latent, Secondary Early, Secondary Recurrent, Sero-Positive Primary, Sero-Negative Primary)	67 (30.6%)	21 (13.5%)	103 (25.8%)
Latent Late (Syphilis of two or more years' standing with no manifestations but a positive blood Wassermann)	65 (29.7%)	71 (48.0%)	84 (21%)
Late Syphilis (Visceral, Skin, Eye, Bone, Cardiovascular, Upper Respiratory Tract)	11 (5.0%)	15 (10%)	25 (6.2%)
Neurosyphilis	76 (34.7%)	41 (27.7%)	188 (47.0%)

* An additional 33 cases were reviewed in which one or more pregnancies had occurred prior to the syphilitic infection. In this group, 42 per cent showed some form of early syphilis, 12 per cent with some form of late syphilis other than neurosyphilis, and 46 per cent with neurosyphilis. The group is too small to warrant interpretive conclusions and is excluded from the above figures, but accounts for the total of 800 cases.

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† In the group of multipara are included only those women with a history of one or more pregnancies, of at least five months' duration, subsequent to their syphilitic infection.

Discussion

An analysis of this table reveals some important differences in the three groups of patients worthy of special comment.

(1) In early syphilis the highest percentage of cases (30.6 per cent) occurs in the nullipara in contrast to a slightly lower percentage in males (25.8 per cent) and a very much lower percentage in multipara (13.5 per cent). Obviously the most important reason for the differences between the groups of multipara and nullipara is the fact that pregnancy often suppresses the manifestations of early syphilis. In addition, as we have shown in the previous paper, the nullipara come for examination at an earlier age. They are, as a class, generally unmarried and are more frequently exposed to infection than the multipara. Eleven per cent were detected as the result of yearly exclusion examinations for venereal disease. In contrast, multipara are most often married, come for examination at a later age, actually are less open to exposure, and usually less concerned over the possibility of infection.

The incidence of early syphilis in males was 25.8 per cent. The reasons for the difference between this figure and the group of multipara is apparent from the above discussion. It is slightly less than in nullipara, explained chiefly, we believe, because 13 per cent of the males gave a definite history of early syphilis which had been unrecognized or neglected.

(2) In latent syphilis, the highest percentage is found in the multipara, 48 per cent, in contrast to 29.7 per cent in nullipara and 21 per cent in males. The high percentage in multipara is again accounted for mainly by the influence of pregnancy which by its inhibitory influence upon the disease fosters the development of latency. As a result, syphilis is often discovered through accidental incidents, such as the birth of a congenital syphilitic child, repeated miscarriages, or syphilis in the husband. Furthermore it is assumed that pregnancy also gives some kind of immunity against central nervous system invasion by syphilis, with the result that the disease in multipara remains most frequently in a latent stage. Supporting this contention is the fact that neurosyphilis in multipara is less frequent (27.7 per cent) than in either nullipara (34.7 per cent) or males (47.0 per cent). The comparatively low percentage of latent syphilis in males (21 per cent) is accounted for by the high percentage of neurosyphilis in this group.

(3) The late manifestations of syphilis (other than neurosyphilis) appear twice as frequently (10.0 per cent) in multipara as in nullipara (5.0 per cent). Males fall in between these groups (with an incidence of 6.2 per cent). The number of cases in these three groups is so small that we do not feel interpretive conclusions are justified. The figures suggest the possibility that pregnancy does not so adequately protect against late syphilis as neurosyphilis and when the assumed protective mechanism of pregnancy fails, the disease is more severe than when this protection is entirely absent (as in nullipara).

Summary

The analysis of 800 cases of all types of syphilis shows that in the nullipara group 30.6 per cent have early syphilis, 29.7 per cent latent late syphilis, 5.0 per cent late syphilis other than neurosyphilis, and 34.7 per cent neurosyphilis; the multipara group shows 13.5 per cent early syphilis, 48.0 per cent latent late syphilis, 15.0 per cent late syphilis other than neurosyphilis and 27.7 per cent neurosyphilis; the males show 25.8 per cent early syphilis, 21.0 per cent latent late syphilis, 6.2 per cent late syphilis other than neurosyphilis and 47.0 per cent neurosyphilis.

Noteworthy is the high percentage of early syphilis in nullipara, the high percentages of latent syphilis and late syphilis other than neurosyphilis in multipara and the high percentage of neurosyphilis in males. The determining factors in the difference between these groups are probably the influence exerted by pregnancy, the age of examination and the social and marital status of the patients.

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A CLINICAL STUDY OF THE MILD GRADES OF HYPOTHYROIDISM *

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The descriptions of the features of two children in whom no thyroid glands were found at autopsy by Curling [1] in 1850, and of sporadic cretinism in England by Fagge [2] in 1871, stimulated the interest of physicians in a disease hitherto not investigated. Fagge regarded "wasting of the thyroid body" as the probable cause of cretinism and he predicted with remarkable accuracy some of the symptoms that might result from a deficiency in the secretion of the thyroid in adults. Two years later Sir William Gull [3] reported two cases of the cretinoid state developing in adults. In discussing these cases he expressed the hope that "once the attention of the profession is called to these cases, our clinical knowledge of them will in proportion improve." Ord [4] in 1878, being much impressed with the mucin deposits in the subcutaneous tissues of adults, named the disease myxedema. The observations of the Reverdins [5] and of Kocher [6] in Switzerland, and of Semon [7] in England, pointed to an insufficient secretion of the thyroid gland as the cause of myxedema. Finally, the investigations of the committee appointed in 1883 by the Clinical Society of London showed that the disease is caused by changes of a destructive nature in the thyroid gland.

Immediately after the discovery of the cause, it became obvious that the successful treatment depended upon supplying thyroid substance from an external source. Victor Horsley,[8] in 1890, suggested the implantation of thyroid tissue. Following this suggestion Murray [9] conceived the idea of making an extract of sheep's thyroids for subcutaneous injection, and in 1891 he began treating a patient with myxedema with injections. E. L. Fox [10] and H. W. G. MacKenzie,[11] independently of each other, in 1892 began the oral administration of thyroid preparations.

This briefly is the history of the discovery of the cause and of the treatment of myxedema. Of the milder grades of hypothyroidism nothing was known until recent years. With increasing knowledge of the function of the thyroid gland, and with instruments for estimating the basal metabolic rate, we are able to diagnose hypothyroidism earlier and to institute the proper treatment before myxedema develops.

During the past decade a number of articles on the mild grades of hypothyroidism have appeared in the literature. Higgins,[12] in 1925, emphasized dryness of the skin, thin hair, indefinite pains, constipation, localized edema, and headache as symptoms of incipient hypothyroidism in individuals with a moderately decreased metabolic rate. He also stated that some of the patients in his series were nervous and had a rapid pulse rate. McLester,[13]

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From the Medical Department of the Lewis-Gale Hospital.

four years later, mentioned thyroid deficiency as a cause of poor health in a small group of individuals in whom a decreased metabolic rate was the only significant finding. Warfield [14] has called attention to the bizarre nature of the symptoms associated with persistent, even though moderately, decreased metabolic rates. Charles H. Mayo [15] has observed complications, mostly in the circulatory system, developing during the convalescence following surgical operations of any kind upon persons who are sensitive to cold weather, who tend to run a subnormal temperature, and who have a basal metabolic rate ranging between minus 12 and minus 20.

Other clinicians have directed attention to certain obscure symptoms associated with a decreased metabolic rate. Breckinridge [16] stated in 1932 that a mild degree of hypothyroidism is a frequent cause of menorrhagia and metrorrhagia, and that it should be excluded before resorting to the curette, the roentgen-ray, radium or abdominal section in the treatment of these conditions. Thyroid deficiency, however, was known before the days of clinical metabolimetry to be a cause of uterine hemorrhage, for Salzman [17] reported cases that were controlled by the administration of thyroid extract. Hinton [18] mentioned hypothyroidism as a cause of abdominal pains in a small group of patients in whom the roentgen-ray examination and other laboratory procedures showed no evidences of pathological changes in the gastrointestinal tract, the gall-bladder or the urinary system.

Brown [19] regarded mild hypothyroidism as a factor in the causation of chronic constipation of middle life, particularly in women of the obese type who have a lowered metabolic rate. Brown [20] also found a diminished secretion of hydrochloric acid in patients with metabolic rates of minus 20 or lower. Several years ago Lee [21] spoke of the occurrence of vasomotor rhinitis in young adults that could be accounted for only on the basis of a low metabolic rate, and that was completely relieved by the administration of thyroid extract. Lawrence [22] called attention to the loss of weight in contrast with the gain in weight in many patients with hypothyroidism. Hypercholesterinemia and also a partial or complete cessation of creatinine excretion have been found by several investigators [23, 24, 25, 26] in all grades of hypothyroidism in adults and in children. These investigators have suggested that the level of the blood cholesterol might serve as a useful check on the severity of hypothyroidism since the basal rate does not always give a true picture, and the clinical impression is difficult to define. They suggested also that the level of the cholesterol may be a useful guide to the efficacy of thyroid therapy.

In a study of 53 patients with basal metabolic rates ranging between minus 12 and minus 38, and in whom a diagnosis of mild or moderate hypothyroidism was made, we have been impressed first, with the vague, indefinite character of the symptoms in contrast with the definite nature of the symptoms of myxedema; second, with the similarity of the symptoms with those either of organic disease or of functional disturbances in the different organs and systems of the body, and third, with the relatively frequent oc-

currence of hypothyroidism here in a section of the country where goiter is commonly seen.

This group does not include patients who in the course of a general examination were found to have a low metabolic rate that improved without thyroid medication. Neither does it include several patients who had symptoms and signs of other endocrine disturbances associated with a low metabolic rate. Nor does it include one patient, a girl 22 years of age, who, at the time of the first examination had what appeared to be a colloid goiter with symptoms suggestive of hyperthyroidism even though the metabolic rate was minus 15. For one and a half years her rate remained constantly below minus 15, then her symptoms became more pronounced and the metabolic rate arose above the normal. Soon afterwards an adenomatous goiter was removed. The following table shows the age incidence:

TABLE I

Age Incidence

Years	No. Cases
10 to 19	4
20 to 29	11
30 to 39	17
40 to 49	15
50 to 59	4
60 to 69	2

It is apparent that the greater number of patients in this series were between 30 and 49 years of age, and that almost an equal number were in the third and fourth decades of life. Females outnumbered the males, 4 to 1.

The appearance of symptoms in the majority of patients during middle life and in the years immediately preceding this period at once raises the question, what is the cause of hypothyroidism? The factors concerned in the etiology have not been satisfactorily determined. Plummer suggested atrophy of the thyroid gland, as a result perhaps of thyroiditis. Hertoghe [27] reported a great frequency of hypertrophied tonsils and adenoids in his cases of thyroid insufficiency. It is doubtful whether infections in the nasopharynx play a part in the causation of hypothyroidism, but since they are frequently found in children and young adults, it is possible that they may, in some instances, affect the thyroid gland causing inflammation and destructive changes, followed by atrophy. It is conceivable that during the earlier stages of atrophy the gland may still be able to secrete sufficient thyroxin to maintain the normal amount in the body tissues for some years, but as the stress and strain of life increase the supply diminishes, and the individual sooner or later becomes conscious of a sense of ill-being. Furthermore, it is possible that an illness producing toxemia, as toxemia of pregnancy, or puerperal infection, or influenza, may damage the gland to such an extent that it does not fully recover. We were unable, however, to obtain from our patients a history of an infection which we thought might have played a part in causing hypothyroidism. We are inclined to believe a constitutional

factor is operative in many of these patients whether or not they have a focus of infection. That there is a constitutional factor seems to be borne out by the fact that some people with hypothyroidism do not have symptoms.

Symptoms. No definite symptoms or signs characterize the mild grades of hypothyroidism. In some cases the history seems an almost interminable story of disconnected symptoms; in other cases the symptoms are few and they may or may not be suggestive of hypothyroidism. The one symptom mentioned by nearly all of these patients, either voluntarily or upon close questioning, is ease of fatigue following mental or physical exertion. Many of these people hold responsible positions; although they are energetic, their work becomes burdensome and they are conscious of having to drive themselves to their tasks. A long rest makes them feel better, but after resuming their work the same weariness comes over them each day. Many of our patients with metabolic rates between minus 12 and minus 20 complained of being more easily fatigued than those with still lower rates.

In addition to fatigue, the chief complaint of one half the patients comprised varying degrees of mental depression, nervousness and irritability. These patients worried over the possible loss of their positions because they felt unable to render efficient service. Insomnia was complained of more frequently than drowsiness, even by those with the lowest basal rates.

Palpitation on exertion was conspicuous among the symptoms related by 20 patients; it was the chief complaint of three. The history of rapid heart action, fatigue and nervousness often suggested neuro-circulatory asthenia. One patient, a business man, 33 years of age, complained only of having had attacks of precordial pain for one month. The pain occurred more often late in the day or during the night, radiated into the left shoulder and arm, was accompanied by a sensation of a "heavy weight on the chest," and on two occasions it was only partially relieved by morphine.

Vague gastrointestinal disturbances, such as loss of appetite, fullness after meals, gas formation, abdominal distention, and occasionally nausea, are noted frequently in the histories. Two patients also complained of dull aching pains alternating with cramp-like pains in the lower abdomen, and another had had a dull pain in the left hypochondrium for six weeks. Constipation was also a common complaint, though it is doubtful whether it occurred much more frequently among the patients in this group than in a similar number suffering with other conditions.

Fourteen patients under 40 years and one past 60 years of age felt much concerned over a gradual loss of eight to twelve pounds in weight. Twelve patients above the age of 40 complained of a gradual increase in weight during the two preceding years even though they restricted their diets. The youngest patient in the group, a girl 12 years old, was brought by her mother for examination to determine the cause of an excessive gain in weight.

Eighteen patients mentioned headache, beginning usually in the vertex and radiating into the suboccipital region, as a prominent symptom. In two cases the headache was distinctly migrainous in character. In addition to

general weakness, four patients under 30 years of age complained of vague pains either in the joints or in the muscles. These pains simulated those due to foci of infections. Twelve patients admitted then were susceptible to colds; eight stated that they suffered with cold hands and feet. One complained only of a dry, itching skin. Three gave a history of irregular menstrual periods; in one the periods came on every two to three weeks and sometimes were profuse, while in two the periods often were delayed three or four weeks.

The average duration of symptoms in all cases was two and one-half years. Not infrequently the patient gave the impression of being neurotic, and in a few a neurotic element was present though it faded out of the clinical picture as the condition of the patient improved.

Physical Findings. Hypothyroidism is found in both the sthenic and asthenic individual, though a larger number of our patients were of the asthenic type. Few had the calm, complacent or indifferent attitude usually observed in patients with myxedema. The majority of the patients appeared to be tired, yet they brightened up and for a time showed an interest in conversation.

Sixteen patients under 35 years of age were found to be definitely underweight, while two, including the girl 12 years old, were overweight. Twelve patients past 40 years of age were overweight, and two underweight. This finding would seem to indicate a tendency towards underweight in patients in whom a moderate degree of hypothyroidism manifests itself in the first half of life, and obesity in the second half. While difficult to explain, it seems logical to assume that during the developmental period of life, when the relative nutritive requirements of the body are at their maximum, any impairment of the oxidative processes of the body might result in a loss of weight. In other words, during this period of life the processes of anabolism are in excess of those of catabolism, and any reduction in the former might upset this balance, and result, therefore, in a retrograde effect.[28] This, of course, is purely a supposition. There seemed to be no relationship between the weight and the degree of thyroid insufficiency in our patients.

Equally interesting was the condition of the skin. Thickening of the integument was observed in seven patients above the age of 35, and in two between 20 and 25 years of age. Each of these patients, with one exception, had a basal rate ranging between minus 15 and minus 22. The exception was a patient with a rate of minus 32. The thick, smooth, papery feeling of the skin was the only manifestation of myxedema found in the entire group of patients. The changes in the integument, like the body weight, seemed to bear no definite relationship to the metabolic rate. It is interesting to note that the skin of another patient became thick, smooth and tight during the interval of two years when she failed to take thyroid extract. On the original examination in 1929 when the metabolic rate was minus 20, the skin felt normal. Two grains of thyroid extract daily maintained a normal

rate for three years. Then as she was feeling well she discontinued taking the drug. When she returned for examination two years later on account of a recurrence of symptoms, her skin had undergone the changes seen in a severe grade of hypothyroidism, although the basal rate was minus 20, as it had been five years previously. Thyroid extract again increased the metabolic rate, brought about relief from symptoms, and much improvement in the condition of the skin.

Moderate dryness of the skin, sometimes with desquamation on exposed surfaces, was found in 20 patients, a few fine wrinkles on the foreheads of several in the third and fourth decades of life, coarse wrinkles in one 25 years old, and in four past 40 years. Thinning and falling of the hair was found in several middle aged or past, but not to any greater extent, as far as we could tell, than is commonly seen at that time of life.

The rate of the heart varied in this as in any group of patients. Rates below 60 per minute were not found, although on the other hand, a moderate acceleration on several consecutive examinations after the patients had rested, was noted in 10 cases, including three with the lowest basal rates. The quality of the sounds varied as in other patients of the same age. The most striking change in the quality of the sounds was found in the young man who complained of attacks of precordial pain. His sounds were distant, the valvular element of the first sound predominated, the rate was 104, and the blood pressure 94 systolic and 60 diastolic. These findings and the history of precordial pain led us to suspect heart disease, even though the patient was young and gave no history of having had an infection that predisposes to cardiac disease. Two weeks of rest in bed and the administration of digitalis to the point of tolerance, however, did not bring about any improvement in the quality of the sounds, or any reduction in the rate. Then we thought of the possibility of hypothyroidism, but going further into the history we failed to elicit any suggestive symptoms. His metabolic rate nevertheless was found to be minus 28. Following the administration of thyroid extract the heart rate became normal, the quality of the sounds became normal, the blood pressure arose nearly to the normal level, and the pains ceased.

Eighteen of the 53 patients had a systolic blood pressure of 110 millimeters of mercury or less, with a proportionate reduction in the diastolic. While low blood pressure may often be associated with hypothyroidism, yet we do not think it was the cause of the hypotension in five patients as there was no significant elevation of the pressure following improvement in their metabolic rates and in their general condition.

The highest pressure, 190 systolic and 106 diastolic, was found in a woman 40 years of age, with a metabolic rate of minus 22. During the four years that she has taken thyroid extract the level of the blood pressure has continued practically unchanged. Another patient, 60 years of age, gave a history of having had hypertension for several years prior to our examination in 1929. At that time the pressure was 180 systolic and 100

diastolic, and the metabolic rate minus 24. She too has had to take thyroid extract most of the time. Her blood pressure has gradually come down to within normal limits, though she is subject to paroxysmal elevations which cause dizziness, headaches and unsteadiness of gait for three or four days. We do not think that there is any relationship in her case between the hypothyroidism and the hypertension.

Five patients between 25 and 40 years of age, and one 60 years old had visceroptosis, the greater curvature of the stomach lying well below the interiliac line, and the colon lying low in the pelvis. Since it is well known that ptosis of the stomach and colon may cause digestive disturbances, and lack of endurance, and since it is also known that people with visceroptosis sometimes have hypotension and low metabolic rates, the question as to what part the ptosis played in causing the symptoms arose in each case. Here we obtained help from the therapeutic test. Those patients with persistently low metabolic rates did not improve satisfactorily until they had taken thyroid extract, whereas other patients with ptosis and low basal rates not due to thyroid insufficiency improved readily without taking the drug.

Vasomotor rhinitis was found in four patients in early adult life by rhinologists who referred them for a general examination, including tests with allergens. The only significant finding was a low metabolic rate, ranging from minus 14 to minus 20. Thyroid extract brought about complete relief.

Infected tonsils were found in 19 patients, ethmoiditis in four, pyorrhea in four, cholecystitis in seven, and cervicitis in three. When analyzing all findings in each case, the question arose as to what part the focus of infection played in the causation of the symptoms and of the low metabolic rate? We at first regarded the low rate as being due to general weakness, secondary to the absorption of toxin over a long period of time and aggravated by the patient's mode of living. No satisfactory improvement was observed, however, in the majority of cases, following the usual methods of treatment and the clearing up of the foci of infection. Soon after the administration of thyroid extract each patient began improving and continued to improve until all symptoms subsided and the metabolic rate was normal. There seemed to be no significant difference in the subsequent course of the patients from whom the foci were removed as compared either with the patients from whom the foci were not removed, or with those who had no demonstrable foci.

Laboratory Findings. A moderate reduction in the erythrocytes or in the hemoglobin content or in both was found in one-third of the cases. A larger number of patients appeared to be anemic. Blood sugar estimations in 11 cases showed a normal sugar content. While this number is small, yet the figures do not indicate a hypoglycemic tendency such as Lawrence and Rowe [29] found in their patients with mild or moderate degrees of hypothyroidism. Estimation of the blood calcium of five patients, including those who had vasomotor rhinitis, showed a normal calcium content. One

of these patients five years later had a calcium content of 8.1 mg. per 100 c.c. blood. Blood urea estimations in eight patients showed normal figures. We did not estimate the cholesterol content of the blood or the amount of creatine excreted in the urine of any patient.

Analysis of the stomach contents of 20 patients with gastrointestinal complaints showed a normal amount of hydrochloric acid in four, hypochlorhydria in 12 and hyperchlorhydria in one. The roentgen-ray examination showed visceroptosis in five cases and hypoperistalsis in one. Reexamination of the gastrointestinal tract of the latter patient 10 weeks later showed normal peristalsis. Presumably the improvement in the rate of peristalsis was due to thyroid extract which is known to increase the tone of the muscles of the intestine. Cholecystograms of seven patients with symptoms and signs suggestive of cholecystitis showed mild disturbances in the function of the gall-bladder.

The roentgen-ray examination of all patients who complained especially of palpitation, and also of the patient who complained of precordial pain, revealed no abnormality in the size or the shape of the heart, and no evidence of disease in the lungs. The electrocardiograms of these patients also were normal.

The urinalyses were normal except for a trace of albumin in several cases.

The one constant finding was a low metabolic rate ranging, as stated above, between minus 12 and minus 38.

Diagnosis. We are aware of the criticism that may be directed against a diagnosis of hypothyroidism when the basal rate is as near the normal as minus 15. A diagnosis in these cases as well as in many with still lower rates can be made only after a prolonged period of observation. A rate of minus 12 or 15, and sometimes one falling within the lower limits of the normal range, may be significant, especially if associated with clinical evidences of a decreased energy production. Although it is unwise to make a diagnosis on the basal rate alone when it is only moderately decreased, still we believe a diagnosis is justified when the rate is persistently low, when it is associated with symptoms among which ease of fatigue is prominent, and when an improvement in both the rate and the symptoms is observed following the administration of thyroid extract. It does not seem necessary to make numerous laboratory examinations; in fact the average patient in private practice will not submit to numerous tests. It is not possible always to correlate the metabolic rate with the symptoms, for many patients with a moderately decreased rate have more pronounced symptoms than those with lower rates.

Hypothyroidism must be differentiated from hypopituitarism, hypoovarianism, hyposuprarenalism, and starvation which all sometimes cause low metabolic rates. It must also be differentiated in some cases from neurocirculatory asthenia, but more frequently from neurasthenia and tuberculosis. In a few of our cases the symptoms were so strongly suggestive

of hyperthyroidism that we were rather surprised to find the basal rate decreased instead of increased.

Treatment. The dose of thyroid extract or of the desiccated gland necessarily will vary according to the basal metabolic rate and the intensity of the symptoms. We usually prescribe from two to six grains daily, occasionally larger doses, rechecking the metabolic rate in about two weeks, and thereafter at such intervals as indicated. The subsequent dose of the drug will depend upon the improvement in the symptoms and in the metabolic rate. The response to treatment varied greatly in our patients. In some a prompt improvement was observed in both the symptoms and the rate, while in other cases the improvement was slow. Sometimes the symptoms subsided before the basal rate returned to the normal, and sometimes they persisted in a milder form after a normal rate was obtained. As a rule, the maximum improvement was not observed in our patients until their rates had been normal or nearly normal for several weeks. About one-half of these cases have not had to take the drug continuously; they have done well when leaving it off for intervals of a few weeks or occasionally for a few months, although if they go for longer intervals without taking it their symptoms recur. A few of these patients have learned from experience when to resume taking the drug. It is usually necessary also to prescribe mild sedatives, a mild laxative, dilute hydrochloric acid, and mild analgesics. Obviously these drugs are prescribed for the relief of the particular symptoms of which the patient complains and they may be discontinued in a few weeks. They may be needed again in the event of a recurrence of the symptoms.

Patients with hypothyroidism should be advised to rest regularly during the day and to retire early at night. The amount of rest naturally will depend upon the kind of work the patient is doing, the severity of the symptoms, and the metabolic rate. In some cases a complete rest for a few weeks is advisable; in the majority, however, this is not necessary.

In addition to prescribing drugs and regulating the habits, optimism is essential in the care of these patients. While thyroid substance will increase their strength, yet encouragement given by the physician carries them more easily through weary hours, gives them a brighter outlook and makes them happier. Life becomes more enjoyable as their ability to render more efficient service increases. And, what gives the physician greater satisfaction than helping his patient regain health and carry on his work more easily? The expression of gratitude of many of these patients calls to mind the words of John R. Oliver,[30] who said: "To a physician, however, there is no pleasanter association or memory than the commingling of a past dependency and a present friendship."

Conclusions

1. Mild to severe grades of hypothyroidism are seen relatively frequently.

2. There are no pathognomonic symptoms or signs. The most frequent and the most important single symptom is ease of fatigue. Other symptoms frequently mentioned are nervousness, palpitation, digestive disturbances, constipation, and various aches and pains. A loss of weight is often found in patients in whom thyroid insufficiency manifests itself in the first half of life and an increase in weight in those affected in later years. Mild grades of hypothyroidism may also be the cause of a few pronounced symptoms as vasomotor rhinitis and pains simulating those of heart disease. A thorough and comprehensive examination must be made in all cases.

3. A diagnosis is justified only when the symptoms are associated with a decreased metabolic rate. Often, however, the patient must be observed over a period of time before a diagnosis can be made.

4. The mild grades of hypothyroidism must be differentiated from other endocrine disturbances, such as hypopituitarism, hypoövarianism and hyposuprarenalism; from chronic diseases such as tuberculosis, and from functional disturbances such as the neuroses and neurocirculatory asthenia.

5. The treatment consists of more than the administration of thyroid substance. Drugs for symptomatic relief should also be prescribed until the particular symptoms of which the patients complain subside. Rest and optimism are also important in the treatment. The maintenance dose of thyroid substance will depend upon the patient's sense of well being and the basal metabolic rate. The sense of well being will depend upon maintaining an adequate supply of thyroxin in the body tissues.

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PERNICIOUS ANEMIA WITH NORMAL BLOOD PICTURE *

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It appears established, from the experiments of Castle and his coworkers,[1, 2, 3] that pernicious anemia is a deficiency disease due to the absence of an intrinsic factor of undetermined nature in the gastric secretion. This intrinsic factor is definitely not hydrochloric acid, though its absence is practically always associated with absence of free hydrochloric acid in the stomach contents. It is well known that this deficiency exerts its influence chiefly on the blood-forming organs and the nervous system. It is a fact, though in my opinion not uniformly appreciated by clinicians and hematologists, that these two systems may be affected concurrently or entirely independently of each other. McCann and Maitland-Jones [4] state that the cord symptoms may be primary and predominant and may occur in pernicious anemia without other symptoms and without changes in the blood picture. The opinion of Ordway and Gorham [5] is that the neurological signs may precede the onset of the appearance of the anemia by years. Davidson and Gulland [6] state that cases of pure subacute combined degeneration occur in which no anemia may be present at all and many patients die from the pathological changes in the spinal cord at a time when the blood picture may be only slightly affected.

The pathogenesis of neurological involvement in pernicious anemia is not known. It is no longer considered a tenable theory that the neurological lesions are a direct result of the anemia per se since, as stated above, it may occur in cases without anemia and many patients with severe anemia present little or no evidence of neurological involvement. Davidson and Gulland believe that there is a constitutional factor in pernicious anemia, meaning that the central nervous systems of certain patients are unable to stand stress and strain to a normal degree. If true, this would explain why the neurological manifestations predominate in some and anemia in others.

The incidence of neurological involvement in pernicious anemia has been variously estimated at from 5 to 80 per cent. It seems that this discrepancy may be accounted for by a difference of opinion as to what constitutes neurological involvement. If only those cases are included in which at autopsy gross and microscopic changes can be demonstrated in the cord, perhaps 5 per cent is a fair estimate. On the other hand, if paresthesias, such as numbness and tingling of the hands and feet, are considered evidences of neurological involvement, certainly 80 per cent is not too high. It has been stated that many of the neurological manifestations are due to toxic causes and that normal function returns with the removal of these causes. Similar phenomena occur in other toxic states. For example, the positive Babinski

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reaction in certain uremic patients becomes negative when the uremia disappears. No figures are available relative to the incidence of neurological manifestations of pernicious anemia associated with normal blood pictures.

The neurologic lesion in pernicious anemia consists chiefly of subacute combined degeneration of the cord, though in many instances the brain, and perhaps also the peripheral nerves, are involved. Grossly, the cord is enlarged, due partly to edema. Microscopically, the degeneration is seen to occur in patches which may increase in size and coalesce. These patches appear first in the white matter, generally in the posterior columns, and later in the lateral columns. Finally the gray matter is involved, but this is a result of injury to the tracts previously diseased. In the late stages, the anterior columns may also become affected. The lesion occurs first in the lower thoracic region, from which area it spreads both up and down the cord.

The neurologic manifestations vary greatly, depending upon the location and extent of the pathologic process. Paresthesias, such as numbness and tingling in the extremities, burning or coldness, formication, pain and diminished temperature sense, are the most common and usually the earliest symptoms. Ataxia with loss of sense of position and astereognosis are usually later manifestations. Diminution or loss of vibratory sense in the lower extremities is a rather constant sign. The tendon reflexes in the lower extremities are often increased early and in the later stages diminished or absent. The abdominal and cremasteric reflexes are usually diminished or absent. A positive Romberg's sign is often present and a positive Babinski's sign is less frequently so. In Woltmann's [7] analysis of 150 cases of pernicious anemia, he found paresthesia present in 80 per cent; vibratory sense diminished or absent in 96 per cent; knee jerks increased in 39 per cent, diminished or absent in 36 per cent and unequal in 14 per cent; Achilles tendon reflex was increased in 23 per cent, diminished or absent in 67 per cent and unequal in 11 per cent; Romberg's sign was found in 52 per cent. He also found multiple neuritis in addition to evidence of spinal cord lesions in 5 per cent of cases.

As examples of patients manifesting neurologic evidences of pernicious anemia without alteration of the blood picture, the following case reports are briefly submitted, with negative and irrelevant data purposely omitted:

Case Reports

Case 1. Mrs. J. L. W., 55 years of age, was first seen June 12, 1933, complaining of diarrhea, numbness and tingling of the hands and feet and weakness. The diarrhea had been present more or less continuously for several years, but had been very much worse for the preceding three or four months. It occurred chiefly from midnight to noon, during which time 20 to 40 stools were passed, the frequency of defecation preventing sleep. Considerable griping, cramping and tenesmus were present. The stools contained much mucus, but no blood. Previous examinations had disclosed the absence of free hydrochloric acid in the stomach contents, and hydrochloric acid had been taken over prolonged periods without relief of symptoms.

Numbness and tingling of the extremities, occurring in cycles, had been present for several years. Weakness was profound, rendering the patient unable to attend to any of her household duties. Moderate unsteadiness of gait had been present, chiefly noted when walking in the dark. She complained of attacks of dizziness, principally on change of position, but also sometimes when lying in bed.

General physical examination disclosed only moderate obesity and mild hypertension, the blood pressure being 170 systolic and 100 diastolic. Neurologically, the knee jerks were equal and exaggerated; the vibratory sense was markedly diminished in the lower extremities and Romberg's sign was positive. Examinations of urine and stools were negative. Gastric contents contained no free hydrochloric acid. The blood picture was normal (table 1) except for a slight leukopenia and a relative lymphocytosis. Roentgenologic examination of sinuses, chest, gall-bladder and gastrointestinal tract disclosed nothing abnormal except for very rapid emptying of the colon. Barium enema disclosed no filling defects.

TABLE I

Case	R.B.C.	Hgb.	C.V.	W.B.C.	Lymph.	Aniso.	Poikil.	M.C.V.	M.C.H.
I.....	5.1	14.5	40	5,400	52%	—	—	78	28.5
II.....	4.5	12.5	37	7,400	39%	—	—	82.2	27.8
III.....	5.0	13.5	42	7,600	25%	—	—	84	27

R.B.C.—Red cell count in millions. Hgb.—Hemoglobin in grams per 100 c.c. of blood. C.V.—Volume of packed cells per 100 c.c. of blood. M.C.V.—Mean corpuscular volume (cubic microns). M.C.H.—Mean corpuscular hemoglobin (micromicrograms).

With the administration of liver extract, the patient has remained almost entirely symptom free over a period of 15 months.

Case 2. Mrs. D. M., 38 years old, was seen on July 26, 1933, complaining of weakness, headaches, numbness below the elbows and knees, shortness of breath, nervousness and dizziness. These symptoms began five months previously, and had become progressively worse. Similar symptoms were present in 1929, continued about two months and disappeared spontaneously.

General physical examination was negative. Neurological examination disclosed exaggerated knee jerks, diminished vibratory sense and positive Romberg's sign. The blood picture was entirely normal (table 1). Gastric contents contained no free hydrochloric acid. The spinal fluid was examined and rather extensive roentgenologic studies were made, but no other abnormalities were detected.

For five months the patient was given dilute hydrochloric acid and treated more or less symptomatically, but no improvement occurred. In January 1934, liver extract was begun, followed within two weeks by almost complete amelioration of symptoms.

Case 3. Mrs. B. S. G., 47 years of age, was first seen May 7, 1934, complaining of neuritic pains over the back and liver region, digestive disturbances, profound weakness, numbness and tingling of the hands and feet, sore tongue, slight fever and slight loss of weight. Symptoms had been present about six months and had become progressively worse, but similar attacks had occurred over a period of at least 10 years. The digestive symptoms consisted of irregular appetite, nausea and vomiting which were present at some time every day, and diarrhea.

The tongue had a glazed appearance with definite atrophy of the papillae and a few excoriated areas along the edges. The knee jerks were markedly exaggerated, the vibratory sense was very much diminished and Romberg's sign was positive with a tendency to fall to the right. Marked cutaneous hyperesthesia, and in areas numb-

ness to stroking, were present over the distribution of the sixth to the ninth dorsal nerves on the right. The blood picture was entirely normal (table 1) and all other laboratory tests disclosed nothing abnormal except the gastric analysis, which revealed an absence of free hydrochloric acid. Roentgenologic examinations were made of the teeth, sinuses, chest, gall-bladder, gastrointestinal tract, kidneys and spine with negative results.

Relief of symptoms was prompt and gratifying after institution of liver therapy and has remained so with its continuance.

These three patients presented many symptoms and signs in common. All complained of symptoms over a prolonged period. Remissions and exacerbations were present in all. All complained of profound weakness and numbness and tingling of the hands and feet. Two complained of dizziness and unsteadiness of gait. Two had severe gastrointestinal symptoms, diarrhea being present in both cases and nausea and vomiting in one. Only one complained of sore tongue. All had an absence of free hydrochloric acid in the stomach contents, diminished vibratory sense, exaggerated knee jerks and positive Romberg's sign. One had peripheral neuritis. All had normal blood pictures, except that one had a slight leukopenia with an increase in the percentage of lymphocytes. All responded symptomatically to liver extract.

It seems likely that too often pernicious anemia is not considered a possible diagnosis because there is no reduction in the number of red blood cells. Undoubtedly, the most constant single finding in pernicious anemia is achlorhydria. Any patient with an absence of free hydrochloric acid in the stomach contents, complaining of symptoms of pernicious anemia and presenting some evidences of neurological involvement characteristic of that disease, in whom no other cause of disability can be detected by thorough and careful examination, should, in my opinion, be given at least a tentative diagnosis of pernicious anemia regardless of the blood picture. He may then have the advantage of liver therapy before irreparable damage has been done to the central nervous system. Even death from subacute combined degeneration may be prevented or postponed thereby.

The effect of liver on the neurological manifestations of pernicious anemia is a subject regarding which there is considerable divergence of opinion. Minot and Murphy [8] stated that neural symptoms in pernicious anemia responded less completely and less readily to treatment than any other accompanying conditions. Davidson and Gulland [6] sound a rather pessimistic note and seem inclined to attribute the subjective improvement, when it occurs, to the effect on the nervous system of the improvement in muscular tone, in the anemia and in the general condition of the patient. Some authors even state that there is a progression of the cord degeneration in spite of, and during, the administration of liver. On the other hand, those who have noted subsidence of the degenerative process with improvement or complete relief of symptoms are too numerous to attribute to mere coincidence or optimism. Tenney and Goldstein [9] have reported a case of

pernicious anemia with psychoneurotic symptoms antedating the development of the anemia by many years in which there was lasting and rapid recession of mental symptoms with the administration of liver extract. Ungley and Suzman [10] reported 61 cases of pernicious anemia with neurological involvement, 30 of whom received adequate liver therapy. Of these 30, five died, eight failed to improve or became worse and 17 improved. The improvement in some of these was sufficiently marked to enable them to resume work in the ship-building yards, whereas, previous to treatment, they had been bed-ridden. Of the 31 cases who received no treatment, 28 died and the remaining three either failed to improve or became worse. Garvey, Levin and Guller,[11] from a series of 47 patients, concluded that liver therapy relieved the neurologic symptoms, but had no effect on the neurologic objective signs. Obviously, we can not expect liver or any other known substance to replace neurones which have already undergone degeneration. However, as has been pointed out, many of the symptoms and some of the signs of neurologic involvement are probably toxic in origin and may disappear if the cause be removed. It appears safe to say that the majority of investigators agree that improvement in neurologic symptoms occurs in most cases and that progression of the degenerative process takes place in very few with adequate liver therapy. This is one of the chief arguments in favor of the necessity for early diagnosis. In my own small series of cases of pernicious anemia, liver therapy has not failed in a single instance to produce improvement in neurologic symptoms. This applies in equal measure to those cases of neurologic involvement without anemia and those with an associated anemia.

Summary

1. The causative factor in pernicious anemia affects chiefly the nervous system and the blood-forming organs. These may be involved concurrently, or either may be affected independently of the other.

2. The pathogenesis and pathology of neurological involvement are briefly discussed and the symptoms and signs reviewed.

3. Three cases of pernicious anemia with neurological involvement and with normal blood pictures are reported. All responded well to liver extract.

4. The effect of liver therapy on the central nervous system involvement in pernicious anemia is discussed and a plea made for early diagnosis and treatment.

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CASE REPORTS

DINITROPHENOL AND RAPIDLY DEVELOPING CATARACTS*

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Chronic obesity decreases efficiency and shortens life expectancy, especially through the increased incidence of cardiovascular disease and diabetes. The control of chronic obesity is therefore a definite and important problem in preventive medicine. Much has been written regarding the cause or causes of chronic obesity but, in the final analysis, obesity results from an excess of energy intake over the energy demands of the body. The control of obesity must lie in a reversal of this relationship with the creation of a deficit on the side of the intake as compared with the expenditure of energy.

To obtain this result, three methods are available: (1) to decrease the energy intake; (2) to increase the energy demands; (3) to combine both procedures. In a large percentage, the obesity is obviously exogenous, due to excessive food intake, and these cases respond readily to moderate dietary restrictions, if faithfully persevered in. There is a second group, the so-called endogenous cases, in which the obesity results more from a disturbed metabolism with decreased energy demands than from an excessive food intake. Some of these cases are associated with well-recognized endocrine disturbances, such as thyroid or pituitary; others, however, cannot be connected with any as yet known endocrine disturbance.

In both groups, but especially in the latter, it is frequently necessary to reduce the caloric intake to such a low point that the patient becomes discouraged and gives up all effort at dietary control. In properly selected cases, satisfactory results are frequently obtained by supplementing the dietary restrictions with various endocrine preparations. There still remains a large group in which the results are unsatisfactory, either because of failure on the part of the patient to decrease the caloric intake, or because of failure of the endocrine preparations or other procedures sufficiently to increase the energy demands.

There is obviously a place for a safe metabolic stimulant that can be administered by mouth and that is free from the unpleasant symptoms, inconvenience, and expense attendant upon the use of the present endocrine preparations. This want seemed to have been satisfied when Cutting, Mehrtens, and Tainter reported on their studies of dinitrophenol in 1933. Here was a drug capable of markedly stimulating the metabolic rate; after exhaustive animal and careful clinical study apparently free from serious deleterious effect upon the human organism when given in proper dosage; and, finally, effectual on oral administration. In some cases it caused skin irritation which, however, promptly cleared on discontinuing the drug. A few adverse reports appeared but these were explained on the basis of coincidence, excessive dosage, or unusual idiosyncrasy.

The drug rapidly gained wide acceptance, both with the profession and with the laity. Because of its marked potency and the occurrence of several fatal cases from overdosage either accidentally or intentionally self-administered, in

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California dinitrophenol was placed on the list of dangerous drugs and could be sold only on the physician's prescription. However, as reported by Dr. Geiger, even when taken in marked excess, a fatal termination could be prevented by immersing the patient in a cold bath. The drug was studied and used extensively, both here and abroad, and although the very conservative were inclined to await the verdict of time before adopting it, it was generally believed that under controlled conditions, dinitrophenol was free from danger, and that, combined with dietary restrictions, it was of definite value in obtaining weight loss in refractory cases under ambulatory conditions. It proved of especial value in producing a prompt drop in weight, so encouraging the patient to persist more faithfully in the dietary restrictions. Strang and Evans in a recent study, although advising against its continued use, state that "no symptoms other than cutaneous were noted that could consistently be attributed to the use of the drug."

Thus matters stood until about the middle of May, when a case that had been under treatment by Dr. R. B. Jones complained of dimness of vision and was found to have cataracts.

Case Reports

Case 1. Mrs. L., aged 50, was started on sodium dinitrophenol October 20, 1933, beginning with 100 mg. per day and gradually increasing to 500 mg. per day for a total dosage of 780 one-hundred milligram capsules and a total weight loss of 49 pounds, going from 237½ to 188½ pounds. The drug was discontinued from March 5, 1934 to May 17, 1934. A second course was given from May 17, 1934 to July 19 for a total weight loss of 17 pounds and a total dosage of 229 one-hundred milligram capsules. The patient maintained her weight at approximately 160 pounds until April 18, 1935 when, with a weight of 164, dinitrophenol was again administered with 200 mg. per day for one week, 300 mg. per day the second week, and finally 400 mg. per day. At this point, dimness of vision was complained of and incipient cataracts were found. The lens opacification increased rapidly, vision was reduced from 0.8 to hand movements at three feet in slightly over one month, and this patient is now awaiting cataract extraction. This patient had received a total of 1072 one-hundred milligram capsules over a period of 18 months.

This case was discussed with Dr. M. L. Tainter who had seen a similar case treated by Dr. A. B. Stockton.

Case 2. A woman, aged 39, had been given dinitrophenol interruptedly over a period of eight or nine months with satisfactory weight reduction. In November 1934, she reported that her vision was getting dim and within 30 days this had progressed to almost complete blindness, and with fully developed cataracts. This patient was operated upon by Dr. Hans Barkan.

With these two cases occurring in relatively young women, although there was no clear evidence that dinitrophenol was responsible, it was impossible to avoid suspicion that in some way the drug was implicated. This suspicion was strengthened when the following case was reported:

Case 3. Mrs. A., aged 36, was treated continuously from January 20, 1934 to July 24, 1934 with a maximum dosage of 500 mg. per day, a total dosage of 910 one-hundred milligram capsules, and a total weight loss of 66½ pounds, going from 222½ to 156 pounds. There was then a period of seven months without dinitrophenol and failure to follow dietary instructions with a resulting gain in weight of 44 pounds. The dinitrophenol was again administered on March 13, gradually increasing to a

maximum dosage of 400 mg. per day for a total dosage of 231 one-hundred milligram capsules and a total weight loss of 12 pounds. The drug was discontinued on May 14 because of the finding of incipient cataracts in both eyes. This patient had a total of 1141 one-hundred milligram capsules of dinitrophenol over a period of 16 months. The opacification progressed rapidly in the right eye so that lens extraction will be necessary. The process has not progressed during three weeks' observation of the left eye.

At this point, three cases of cataract developing in relatively young women who had been taking dinitrophenol were reported by Oakland physicians.

Cases 4, 5 and 6. A woman, about 40 years of age, reported by Dr. J. R. Sharpsteen of Oakland, had been taking dinitrophenol without a physician's supervision for several months. She also has shown rapidly developing cataracts.

Two other cases, reported by Oakland physicians, of rapidly developing cataracts in women who have been taking dinitrophenol.

Routine eye examinations were now made on several cases that had been taking dinitrophenol with the result that out of about 12 cases one other case showed slight changes.

Case 7. Mrs. P., aged 39, started on sodium dinitrophenol March 1, 1934, beginning with 100 mg. per day and gradually increasing to a maximum of 500 mg. per day for a total of 316 one-hundred milligram capsules and a total weight loss of 21¼ pounds. The drug was discontinued from June 26, 1934, but with this relatively short period of treatment and small total dosage, definite but slight lens changes are evident one year later.

Another case recently appeared:

Case 8. Mrs. H., aged 44, took sodium dinitrophenol from November 23, 1933 to April 30, 1934, gradually increasing to a maximum of 500 mg. per day and for a total dosage of approximately 650 one-hundred mg. capsules and a total weight loss of 26 pounds. No dinitrophenol was given after April 1934 but for some months, dimness of vision has been complained of and in June 1935 well-developed cataracts were found.

In all of these cases occurring in relatively young women showing certain unusual and apparently characteristic lens changes and usually progressing rapidly to complete cataract, the only common factors have been dietary restriction and the administration of dinitrophenol. Of course, this association does not prove dinitrophenol the causative agent, but it certainly does indicate that until this entire question is clarified, dinitrophenol must not be administered.

Many questions arise as to why, if dinitrophenol is the causative agent, it has taken 18 months for the signs and symptoms to appear; why, in some, no symptoms have appeared for over a year after discontinuing the drug while in others, symptoms developed in a few months; is the action a direct toxic effect on the lens or indirect through some metabolic change; and is the change associated with the size of the daily dose or the total dosage?

These, and many more questions, demand study and explanation but the answers can wait. At present, the important indication is to discontinue the use of dinitrophenol.

TOXIC REACTION TO ALPHA-DINITRO-ORTHO-CRESOL *

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THE use of the nitrophenol group as a metabolic stimulant has brought to light many reports of toxic reactions [1, 2, 3, 4] and even fatalities.[5] Cutting, Mehrtens and Tainter [2] have sounded a sombre note of warning that the drug is still too new in usage and the various manifestations of toxicity are not known. More recently, Dodds and Pope [6] have reported better results in the treatment of obesity with the use of dinitro-ortho-cresol instead of dinitrophenol. The clinical application of the drug by Dodds and Robertson [7] has shown it to be from three to five times as strong as dinitrophenol, yet apparently of the same toxicity. The dosage advocated by them was from 50 to 100 mg. per day for a normal adult person. As a further check, the basal metabolic rate should never be allowed to exceed plus 50.

We have found no clinical report of a reaction to dinitro-ortho-cresol in the literature, and deemed it of interest to record the findings in our case.

CASE REPORT

P. F., white female, age 14½ years, was admitted to the endocrine clinic in January 1933 for treatment of obesity. A diagnosis of pituitary obesity with secondary hypothyroidism was made, and treatment consisting of thyroid and pituitary extract orally and hypodermic injections of anterior pituitary solution was instituted. She responded well to this therapy together with a high protein, low fat and carbohydrate diet for about six months, lost 14 pounds and grew 2½ inches. During the second half of 1933 she was somewhat lax in her attendance at the clinic and in her diet, and her weight rose from 110 to 122 pounds. In January 1934 she gained rapidly, and did not respond to the former diet and medications. It was decided to use alpha-dinitro-ortho-cresol [3, 4, 5] as a metabolic stimulant, and this was started on April 4, 1934. No other medication was given and her former diet was continued. Her weight at that time was 132 pounds (60 kg.), and a dose of one capsule of 100 mg. of dinitro-ortho-cresol daily was ordered for one week. As there was no resultant loss in weight, the dose was increased to two capsules a day. On April 15, after four days of the increased dosage, the patient awoke, complained of feeling drowsy, and noted a swelling of the fingers and hands. It was found necessary to remove a school ring from the finger because of the swelling. During the day a greenish-yellow color of the sclerae was observed, and the urine was reported to be extremely dark and odorous.

The next day, Monday, April 16, the patient went to school against advice, but was so drowsy that she fell asleep in the classroom. A headache was present at this time, and an itching maculo-papular eruption appeared during the afternoon. That night she was nauseated and vomited several times. In spite of the malaise, she again went to school the following morning, but returned home because of drowsiness, headache, nausea and a ringing sensation in the head which was exaggerated on climbing stairs.

The medication had been discontinued as soon as this train of symptoms set in, but the patient did not return to the clinic until April 18, four days later. The total amount of the drug taken was 15 capsules of 100 mg. each, or 1.5 gm. of dinitro-

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ortho-cresol over a period of 11 days. Physical examination on April 18 revealed a marked icterus of the sclerae, but not of the skin or mucous membrane of the mouth. The pulse rate was 90 per minute, of good volume and normal rhythm. The heart and lungs were normal, there was no liver enlargement or any hepatic tenderness. The general condition was good, no skin rash was present, and there were no other complaints.

Laboratory Examinations: Urine was dark in color, had a strong odor, showed a faint trace of albumin; bile pigment was absent.

Blood count: red blood cells, 4,300,000; hemoglobin, 80 per cent (Sahli); white cells, 6,600; polymorphonuclears, 55 per cent; lymphocytes, 35 per cent; mononuclears, 5 per cent; eosinophiles, 5 per cent. Platelets, 200,000. Bleeding time, 8½ minutes; coagulation time 9 minutes.

Blood chemistry: (mg. per 100 c.c.) glucose 92.7; urea nitrogen 14.8; non-protein nitrogen 27.4; creatinine 1.52; uric acid 3.52; cholesterol 178; chlorides—whole blood 469.7; plasma 592.3; red cells 284.2.

Icteric index 24.75. Van den Bergh reaction negative in both direct and indirect phases.

Reëxamination of the patient one week later, April 25, showed a diminution in the yellow discoloration of the sclerae and urine. There was no loss of weight during this period. On the thirteenth day after the onset of symptoms, the swelling of the fingers and hands recurred, and lasted for an additional 48 hours.

Treatment consisted of local application of calamine and zinc lotion for the rash, and general purgation to hasten excretion of the drug. It was later ascertained that the patient had been eating considerable amounts of candy every day, merely as a whim, and not because of hunger.

Comment

Unfortunately we were unable to obtain a basal metabolic rate on our patient during the acute stage, and to report any later reading would be but fallacious. Of extreme interest are the following features: the greenish-yellow color of the sclerae and no signs of jaundice of the skin or mucous membranes; the extremely dark colored urine showing a negative bile test; and lastly, an icteric index of 24.75 and a negative Van den Bergh reaction, indicating no true hepatic involvement. This clinical picture of "jaundice" is accounted for by the yellow color of the drug itself in solution, and is not astounding when one recalls the deep yellow color of picric acid solution (trinitrophenol), and the close chemical relationship of dinitrocresol to it. The yellow discoloration of the drug in the blood serum can be removed by adding a few drops of a 5 per cent solution of HCl, as advised by Tainter and his co-workers. Isaacs [9] reported such a revised icteric index reading of 5.3 instead of the original one of 20 in Jackson's [1] case of dinitrophenol poisoning. The same chemical reaction holds true for dinitro-ortho-cresol.

Summary

A case of a toxic reaction to alpha-dinitro-ortho-cresol [3, 5] is reported in a girl 14½ years of age. The symptoms manifested were: marked drowsiness, headache, nausea, vomiting, swelling of the fingers and hands, an itching maculopapular rash, yellow colored sclerae and a dark urine. The icteric index was 24.75 (not decolorized) and the Van den Bergh reaction was negative.

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PRIMARY COSTAL OSTEOMYELITIS *

REPORT OF A CASE

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Primary osteomyelitis of the ribs in children is not a common condition in this country judging from reports to be found in the literature. Farr [1] reported five cases in a series of 98 patients with osteomyelitis, and Phemister [2] three in a series of 320 cases.

Ameline,[3] and Parcelier and Chauvenet [4] give credit to Jaboulay for the first description of the disease in 1885, and to Lannelongue for the second published report in 1890. Since the first report Ameline has found in European literature reports of approximately 100 cases in patients of all ages.

Secondary osteomyelitis of ribs is more common. Andreson [5] reported a case in a seven weeks old infant following an upper respiratory infection. Gamboa and Montarcé [6] reported a case of costal and vertebral osteomyelitis in a 40 day old infant following traumatism of the right hip. Coursières [7] reported a case in an infant following typhoid fever. Ameline has found that costal osteomyelitis may follow eruptive fevers particularly varicella, typhus, recurrent, and Malta fevers, and septicemias. Philardeau [8] reported a case in a four and a half year old child following varicella. In their review of 92 cases, Parcelier and Chauvenet found that bacteriologic examination was made in 32 cases and of these 20 were caused by staphylococci, eight by streptococci, two by pneumococci, and one each by a diplococcus and an enterococcus.

Wolf and Ring [9] report one case following otitis media and an evident streptococcic septicemia in a six months old infant.

The diagnosis of costal osteomyelitis is at times difficult to make particularly

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when the posterior portion of an upper rib is involved or the picture is complicated by an empyema. In cases with localized swelling, redness, and tenderness, the diagnosis is more obvious. In cases in which the posterior portion of a rib is involved and in which tenderness and muscle spasm are the only signs, and fever and pain the only symptoms, the clarity of the picture is obscured and one may be left in doubt until secondary manifestations of the infection appear. Roentgen-ray may be of only negative assistance as in the case to be presented.

The treatment advocated by all authors quoted above, except Wolf, is resection of the diseased portion of the rib. Graham [10] reported a complete recovery from a draining sinus following a primary staphylococcic costal osteomyelitis after operation and removal of a sequestrum. Kelley [11] describing variant types of osteomyelitis writes that in mild, subacute, or serous osteomyelitis, operation should be immediate, though in this type, and in typhoidal osteomyelitis the surgical intervention is not usually so extensive as in the acute fulminating types.

The prognosis of acute costal osteomyelitis is probably similar to that of osteomyelitis elsewhere. DaCosta [12] taking his statistics from Kennedy gives a general mortality of 34 per cent for all osteomyelitis, and 10 per cent for those cases operated upon within 44 hours of the initial chill. Ameline in reviewing 96 cases of costal osteomyelitis found a mortality of 9.6 per cent.

In the case to be described here, the course and resolution of the disease presented unusual features.

Case Report

The patient, a nine year old boy, was first seen because of his present illness on June 21, 1933. The mother stated that for about a week he had complained of pain in the region of the right scapula and had had a low fever. There was no history of injury or previous illness in the past year with the exception of varicella six months before. On examination there was moderate tenderness over the fifth right rib posteriorly four inches (10 cm.) from the spine, with some muscle spasm. There was no redness or swelling. His rectal temperature was 101° F. There was no cough, no pain during respiration, nor were any abnormal breath sounds heard. Salicylates were prescribed, and the mother was requested to report her observations of the child's temperature. One week later the child was again seen, and at this time the area of tenderness of the right chest posteriorly was more marked, involving the fourth, fifth, and sixth ribs. The rectal temperature was 102° F. and the respiratory movements of the right chest were somewhat limited. The boy appeared to be more ill than when previously seen. The evening of the twenty-ninth, his temperature went to 105° F. and the following morning the child was sent to the hospital. Stereo roentgenograms were taken of the chest both for bone detail (figure 1) and soft tissues. The ribs appeared normal but there was a pleurisy and early pneumonic infiltration of the upper lobe of the right lung. The white blood cell count at this time was 16,000, of which 82 per cent were polymorphonuclear neutrophiles, and of these 17 per cent were eosinophiles. This large number of eosinophiles is interesting in view of the fact that 48 hours later the patient developed a severe generalized urticaria. A Mantoux tuberculin test with 0.1 mg. O.T. was negative. Following the appearance of the urticaria the temperature dropped to normal and the boy felt quite well except for complaints of pain on movement of the right arm and the neck. The following day the patient began to cough and the temperature in the next 24 hours mounted to 105.8° F. Another roentgen-ray was taken on July 5, the sixth hospital day. This showed a uniform opacity over the entire right chest indicating a definite

pleural effusion. The next day, July 6, thoracentesis was done and 150 c.c. of a slightly cloudy, yellow fluid were obtained, which when cultured produced a pure growth of hemolytic *Staphylococcus aureus*. The course of the patient's illness was quite stormy at this time, the temperature varying between 98° and 104° F., the boy complaining of great pain in the right chest and a severe urticaria coming and going intermittently. An intradermal injection of a suspension of the killed staphylococcus containing six billion bacteria per c.c., obtained from culture of the pleural exudate produced a wheal 1 cm. in diameter surrounded by an area of erythema 6 cm. in

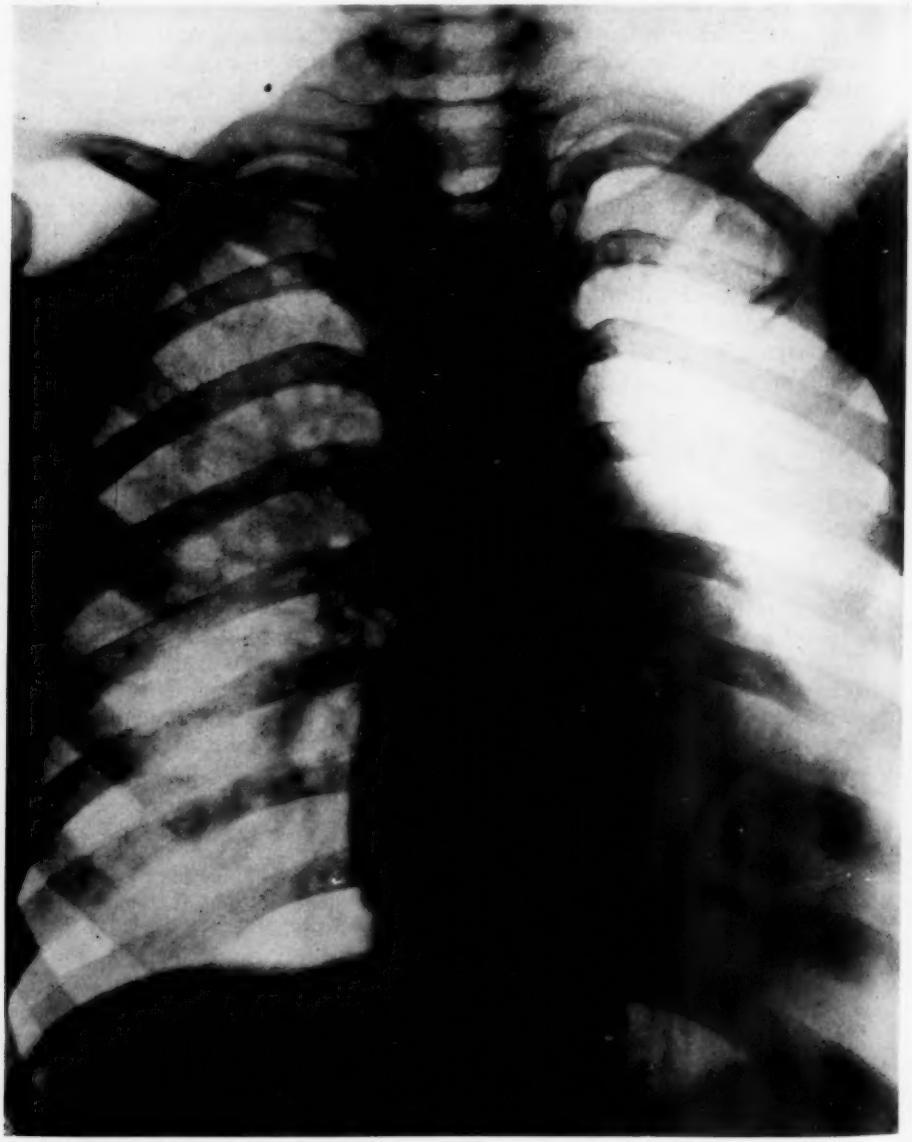

FIG. 1. Early pneumonic infiltration of the upper lobe of the right lung. No evidence of rib involvement.

FIG. 2. Osteomyelitis of the posterior portion of the fifth right rib. Catheter draining the empyema may be seen at the lower left.

diameter. The right pleural cavity was again aspirated on July 8, the ninth hospital day, and 115 c.c. of exudate removed. On July 10, a catheter was inserted in the pleural cavity between the seventh and eighth ribs in the right posterior axillary line for continuous closed drainage. The pleural cavity was irrigated with normal saline two or three times daily. For five days following the institution of continuous drainage the boy complained of such severe pain in the right chest that codeine was

necessary to control it, although his temperature had not risen above 100.8° F. After this time he seemed much more comfortable, his appetite improved, and his temperature varied from 99° to 100° F. On July 31, the thirty-second hospital day, another roentgen-ray (figure 2) was taken to check the progress of the empyema.

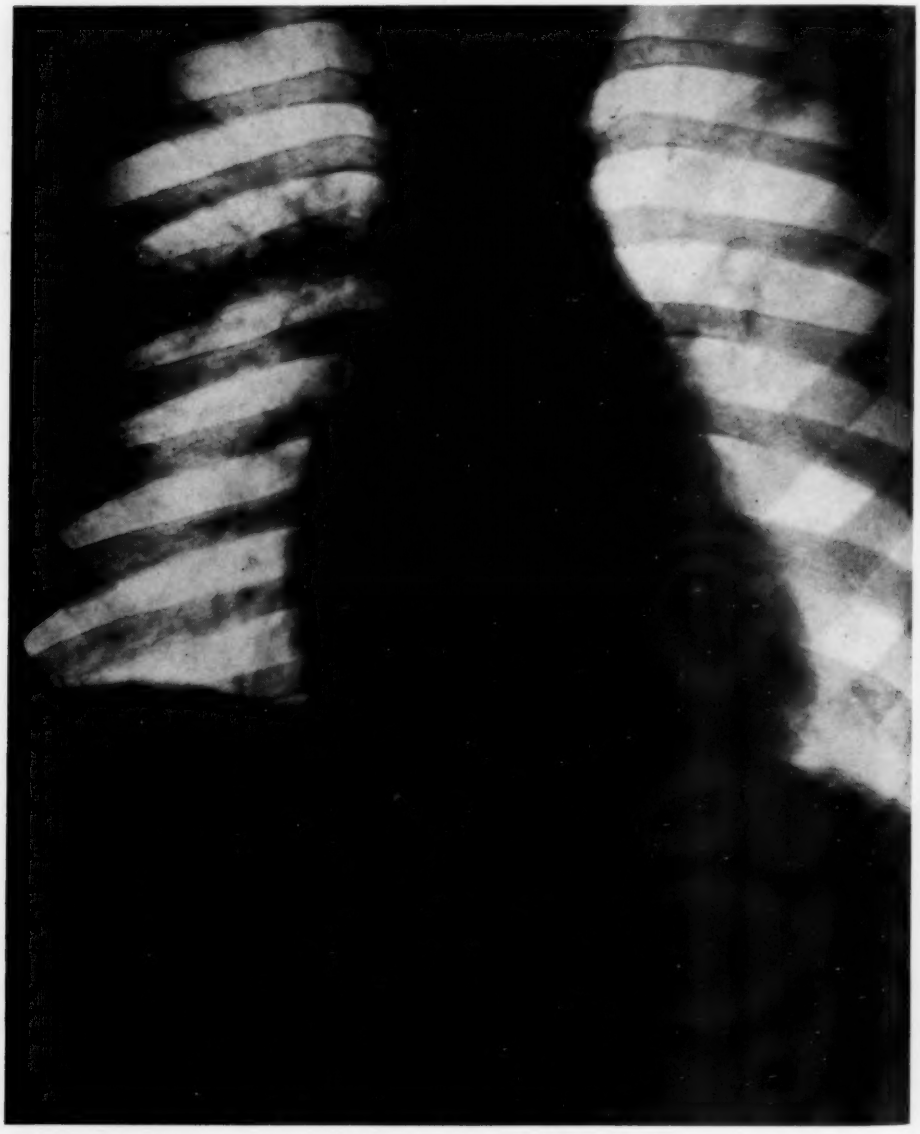

FIG. 3. Healed costal osteomyelitis two and one-half months after onset of the disease.

This showed the pleural cavity to be almost free of fluid and also showed an evident osteomyelitis of the posterior third of the right fifth rib. Because of the clinical improvement manifested by the child and because it seemed reasonable to believe that drainage from the involved rib was occurring through the pleural cavity, it

was felt justifiable to withhold surgical interference until further observations had been made. A roentgen-ray taken 10 days later showed no extension of the process in the rib and there appeared to be some indication of new bone formation along its superior surface. The drainage tube was removed at this time, one month after its

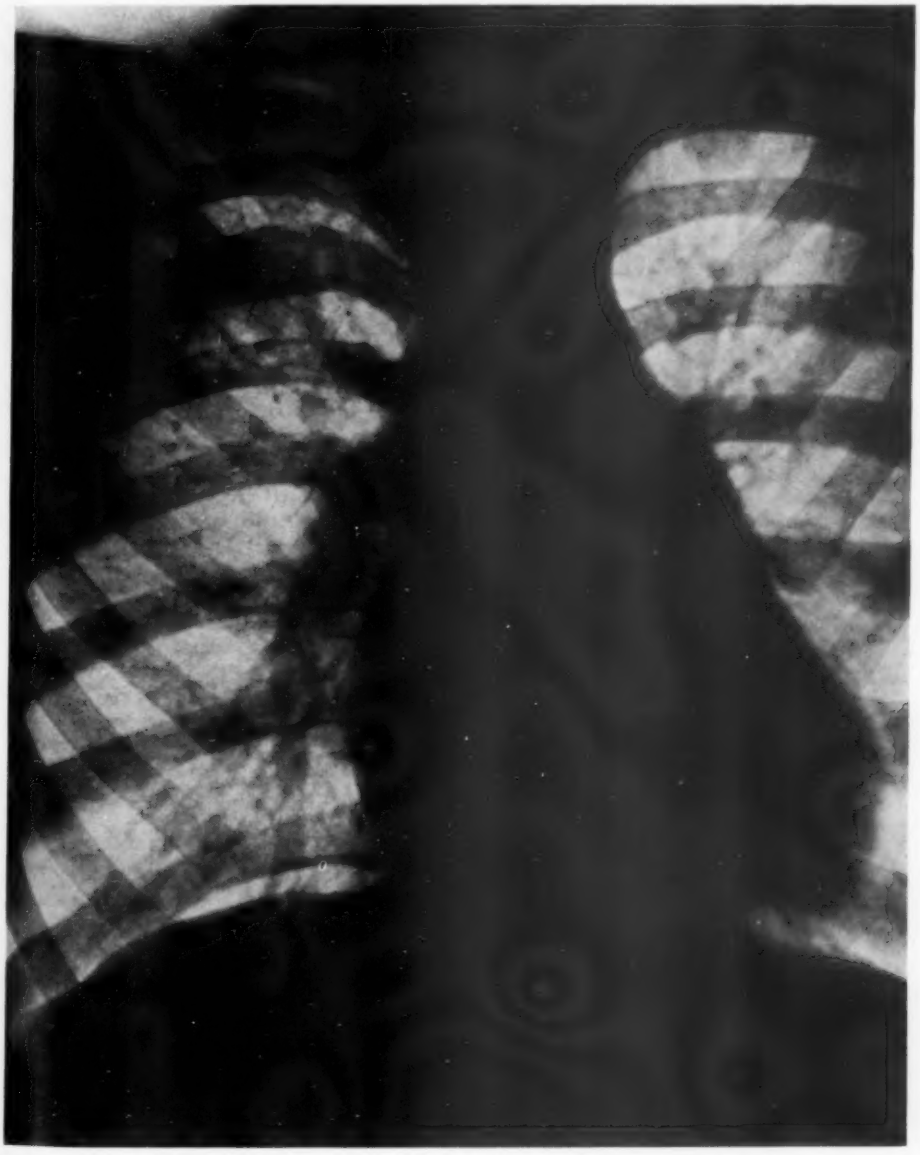

FIG. 4. Healed costal osteomyelitis 15 months after onset of the disease.

insertion, and on the forty-second hospital day. The boy continued to improve and was discharged cured, August 15, after a hospital stay of 48 days. This patient was carefully followed after leaving the hospital and roentgen-rays (figures 3 and 4) were

taken monthly until February 1934, six months after his discharge. These showed progressive filling of the bone defect caused by the osteomyelitis. The boy was examined in July 1934, one year after the onset of his illness and showed at this time a symmetrical chest without visible defects, with no evidence of any activity at the site of his previous costal osteomyelitis.

Summary

A case of osteomyelitis of the posterior third of the fifth right rib is presented which healed without operation, after drainage of the accompanying empyema. Drainage from the infected rib occurred apparently into the pleural cavity contrary to the usual statement in the literature that this does not occur. Wolf has lately reported a similar experience.

The etiologic agent of the infection was a hemolytic *Staphylococcus aureus* to which the patient was sensitized and which produced a severe generalized urticaria.

The first symptoms of primary costal osteomyelitis of the posterior portion of the fifth rib are fever and localized pain. The first signs are local tenderness, muscle spasm, and pleural thickening accompanied by a rapidly developing empyema. Roentgen-ray evidence of infection may not be present until after the empyema develops. Drainage of the osteomyelitis can and does occur into the pleural cavity with spontaneous resolution of the diseased rib.

Note: Dr. Howard Barker, M.D., F.A.C.S., of the Surgical Division, instituted and supervised the drainage of the empyema in the case presented. His assistance is gratefully acknowledged.

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EDITORIAL

OUT-PATIENT CLINIC PROBLEMS OF TODAY

THE character of dispensary work in many cities has changed radically since the inauguration of the Federal program of medical relief. It was provided in that program that medical care in the home and in the physician's office could be paid for from relief funds, but that existing medical institutions such as dispensaries were not to share in these funds but were to continue as a charge upon the private philanthropy or the local tax funds of the community. The effect of these rulings varied in different parts of the country. In some cities the major part of the medical care of the indigent on the relief rolls was undertaken by the general practitioners and there was no increase and perhaps even a decrease in dispensary attendance. In other communities a policy radically opposed to this was adopted. To conserve relief funds all of the "clients" of the relief administration were herded into the dispensaries or onto hospital wards when in need of medical care, and the provisions in the Federal regulations for their medical care in the home and for the payment of their attending physicians were ignored. Apparently neither plan has proved wholly satisfactory to the interested parties, i.e. the relief administrators, the medical institutions, the physicians and the sick people on relief. From these experiences, however, it should be possible to derive some information of interest.

In those cities in which the major part of the medical care of the indigent has been carried out by the general practitioner and has been paid from relief funds there has grown up, at least in the minds of the relief administrators, a realization of the cost of medical care and of the difficulties that arise in avoiding abuses in its administration. In those cities which have attempted to unload the whole problem upon existing medical institutions it has become apparent that such institutions cannot replace the general practitioner. It is perhaps in this last connection that the most instructive lessons concerning dispensaries and their proper functions have been learned.

It has become evident, for example, that a dispensary is no longer a dispensary, and that its adoption of a more modern name, "out-patient clinic," really corresponds to a very fundamental change in its nature. Old-fashioned dispensaries, places of snap-shot diagnosis and pill therapy, would have had less difficulty in handling the swarm of relief cases than the more modern out-patient departments. The majority of their admissions they would have turned away with a clap on the shoulder and an aspirin tablet, a compound cathartic pill or a tonic. Only a few would have been carefully examined. But modern standards in out-patient clinics necessitated a complete history and physical examination on each admission, and at least a urine test, with perhaps a Wassermann test, a blood count and in cases of doubt roentgen-rays and consultations in special clinics. All this was splen-

did but it was not war; and these were like war conditions. Where no adaptations were made the machinery clogged, overworked and disgusted doctors resigned, and the net end result was that the clinic either refused to take more than a given number of relief cases and thereby failed the community, or it disintegrated entirely. In some cities there has been quite a mortality among the smaller dispensaries. The lesson would seem to be that the modern out-patient clinic is not fitted to do general practice. It is a highly organized diagnostic and therapeutic institute for ambulant cases and it holds its volunteer staff together only in proportion to its ability to maintain standards of work which will satisfy the desires of that staff to learn more than they can learn in their own offices. If the emergencies of the present social situation force such an institution into the mass care of large groups of people presenting chiefly minor and simple problems its only salvation lies in adapting its machinery to the new demands. It may be helpful to establish an adequate admitting system which will divert into a Clinic for Minor Illness those cases which do not require the full routine of the major departments. Such a solution is not ideal but it meets the emergency far better than an " appointment system " which turns away many with no care at all, and is apt to admit today a case of chronic constipation while putting off until next week a case of juvenile diabetes.

The physicians in out-patient clinics have suffered not only because of the excessive number of cases admitted, and because so many of these cases presented only minor disorders, but also because they have had to settle problems of a type which distressed and did not interest them. Too often after a history of vague complaints had been recorded and an essentially negative physical examination performed the real purpose of the visit to the clinic was found to lie in a desire to be furnished with a certificate of physical inability to work, which might be useful when a " work project " was threatening. The older physician feels that it was one thing, back in the days when he was in the army, to mark a malingerer " duty " at sick call, but another thing to be forced into the uniform of the relief administration and driven to passing judgment upon the indigent when his purpose in coming to the clinic was to aid the sick and to perfect himself in his art. The result of his distaste for the task is probably that he is over-lenient or oversevere—and that he comes a little later on his next day. Such problems of a medical administrative character might well be handled outside of the outpatient clinics by an Examining Board. The clinic should receive only the doubtful cases referred to it for more complete study.

It does not seem probable that the near future will see any marked falling off in out-patient clinic attendance. With the shrinkage of Federal funds for relief those cities which have been paying physicians for caring for the indigent will tend to try caring for them in the free clinics, and those which have already pursued this method will attempt to continue it. It is true that the number of indigents on the relief rolls will diminish as the long heralded " Work Program " comes into effect, but it is equally true that the

scale of wages paid under that program will not furnish the recipients with the means of paying physicians. We shall be seeing them in our clinics next winter. *Plus ça change, plus c'est la même chose.*

The majority of internists are or have been connected with out-patient clinics. In our various communities we should now lend our counsel in the making of plans which will best adapt the out-patient clinic to the rôle it is called on to play.

REVIEWS

The Practitioner's Library of Medicine and Surgery. Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Volume VIII: Therapeutics.* Associate Editor, ALBERT I. SULLIVAN, B.S., M.D., Assistant Professor of Medicine, Yale University School of Medicine. xliv + 1031 pages, 27 illustrations. D. Appleton-Century Company, New York. 1935. Price, $10.00 a volume.

In *Therapeutics,* more than in any other field of medicine, the practitioner has need of a comprehensive, adequately indexed textbook which will give him the well-considered opinions of experts in the management of the various diseases which he may encounter. In the treatment of the more common affections the practitioner of long experience becomes an expert himself, but for the management of the unusual condition he must turn to the advice of others. Thus, whether it be for the student or for the seasoned veteran, such a work as Volume VIII of *The Practitioner's Library* becomes a necessity. This volume, to which there are 35 contributors, combines a presentation of the principles and technic of therapeutics with a consideration of the management of the individual diseases. Part I, which is approximately one-fourth of the book, is devoted to General Therapeutics; Part II, to Special Therapeutics. In the latter the arrangement of subjects is in part etiological and in part anatomical. In the former, dietary, physical and psychotherapeutic, as well as medicinal, measures are considered.

As has been stated in the reviews of the preceding volumes of this series, it is impossible to list the individual contributors or to evaluate the separate chapters. In general, the discussions are characterized by a degree of completeness which indicates liberal space allowances from the publishers. Great care has been taken to assign the topics to recognized experts in the particular fields. This volume could deservedly stand alone as a comprehensive system of therapeutics even if it were not supported by its fellows in the Practitioner's Library.

C. V. W.

Dietetics for the Clinician. By M. A. BRIDGES, B.S., M.D., F.A.C.P. Second Edition. 970 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1935. Price, $10.00.

This is an ambitious treatise and a number of the sections have been prepared by specialists in particular branches. Some of these are very good. There is of necessity in such a large book on diet considerable overlapping and repetition. The principal section (Part II) arranges the various diseases, for convenience, in alphabetic order. Each disease is first the subject of a general discussion, after which sample menus are given, followed by general suggestions. Thus, for Addison's disease, it is recommended that the diet be designed to increase gastric acidity and the oral use of dilute "muriatic acid" is advised. The addition of extra protein to the diet is recommended to combat weakness, and it is said, this "will frequently tend to offset this symptom." Foods of a "bland and alkaline character" are to be omitted. A diet "high in sodium chloride" is recommended since "it has been recently proved that a diet high in sodium chloride serves admirably to maintain the body tissue fluid." Olives, pickles, salted crackers and cheese are recommended. It is, of course, dangerous to rely merely on the salt of the food as adequate for sustaining patients with this disease and one should not intimate that such may be the case. The same criticism applies to the recommendations for the treatment of chlorosis. No one relies merely on a diet high in iron content alone for its treatment and this fact should be made clear.

"Commercial fat-free butter" in "minimal quantities," is suggested in the treatment of acidosis. This preparation is unknown to the reviewer. A diet high in calcium is recommended in the treatment of hemophilia. One would expect this to be about as useful as the estrogenic hormone. The diet in angina pectoris is advised to be that used in "uric-acid diathesis" since there is in this malady, according to the author, "a consistent elevation of the blood uric acid." The treatment of diabetes by Short is concise and clear. The chapter on Bright's disease by Mosenthal is excellent. There is a large section on pediatric feeding by N. I. Saxl.

The appendix, bibliography and index occupy the last quarter of the book, 275 pages. A good discussion of alcoholic beverages, with a table of analyses of their food values and composition, together with detailed description of the qualitative ingredients of many mixed alcoholic drinks, from cocktails to *pousse cafés*, is included. The food tables are very comprehensive and appear to be well arranged. They include many commercial preparations in common use, analyses of which have not appeared elsewhere.

G. A. H.

Child Psychiatry. By LEO KANNER, M.D. 527 pages; 17 × 26 cm. Charles C. Thomas, Baltimore. 1935. Price, $6.00.

In his introduction the author describes the purpose of this book as follows: "The present volume, which is the first textbook of child psychiatry in the English language, is offered as an attempt to cover the entire field of children's personality disorders on a broad, objective, unbiased, and practical basis. It has grown out of everyday contacts with pediatricians, consultation work in a large pediatric clinic and dispensary, collaboration with private practitioners and with the various child-caring agencies of the community . . . , and teaching activities at the Johns Hopkins University School of Medicine. It is intended primarily for physicians and medical students but is also meant to be of help to all those interested in children's behavior problems: social workers, psychologists, sociologists, educators, juvenile court workers, etc."

The book is divided into two parts. The first deals with the principles and methods of psychiatric examination, diagnosis and treatment. In part two the author discusses each clinical entity and complaint which brings a child to a psychiatric clinic, from the point of view of diagnosis, etiology and treatment. Each chapter contains a scholarly historical account of the topic and includes the most important references to the literature. The book, especially the second part, is a useful reference volume. It is liberally supplied with research data from the author's extensive case material. Pediatricians will find it full of practical suggestions for the handling of the behavior and personality problems which they frequently encounter in their practice.

The author has attempted to steer a sane, objective course among the various "schools of thought" which so confuse the student. He has done this so skillfully that the adherents of each school will accuse him of relative neglect of their theories or emphases. The author's leaning is toward the Meyerian school and he gives, in this book, a lucid, readable account of the philosophy and methods of that school, as related to child psychiatry.

H. W. N.

Diabetic Manual for Patients. By HENRY J. JOHN, M.A., M.D., F.A.C.P., Maj. M.R.C. Second Edition. 232 pages; 13 × 20 cm. C. V. Mosby Co., St. Louis. 1934. Price, $2.00.

This manual is stated to be "a non-technical guide for the person suffering with diabetes." The author believes infection and overeating are the most important causes of diabetes and that heredity is "really of little importance so far as the individual case is concerned." Diabetes is more common among Jews, he feels, because they are especially prone to overeat and not because of any inherited taint.

This book should be a valuable aid to the intelligent patient. It contains practical suggestions regarding the construction and preparation of diets, the injection of insulin, the treatment of insulin reactions and other questions which frequently present themselves to the patient.

G. A. H.

Brucella Infections in Animals and Man: Methods of Laboratory Diagnosis. By I. Forest Huddleson, Department of Bacteriology and Hygiene, Michigan State College. 125 pages, 24 illustrations. The Commonwealth Fund, Division of Publication, 41 East 57th St., New York City. Price, $2.25.

This small volume represents a monograph on the laboratory diagnosis of Brucella infections in man and certain susceptible animals. The subject is covered in seven main chapters.

Briefly, chapter one devotes itself to a short natural history of the three forms of this disease; and to the classification, morphology, staining and cultural characteristics of the organisms. Chapter two takes up the methods of isolating Brucella strains of bacteria. Chapter three covers the pathology, of man, cattle and guinea pigs. Chapter four gives the serological methods in common use. Chapter five presents the skin testing or allergic method of diagnosis. Chapter six discusses the opsono-cytophagic power of the blood and its application in diagnosis. Chapter seven discusses the various means at the disposal of laboratory workers for differentiating the three types of Brucellosis. The methods given in these seven short chapters are those which have been found reliable in the author's laboratory. Much of the subject matter represents original work by the author and his coworkers. The remainder represents a selection from the methods of others.

The author has the advantage of a very wide experience with his subject. To his laboratory have come hundreds of strains of the Brucella organism from many parts of the world. His original work in the field has been important. This small monograph is therefore authoritative. It will be of great value to all laboratory workers called upon to assist in the diagnosis of Brucella infections in man or the lower animals.

S. L. J.

COLLEGE NEWS NOTES

Gifts to the College Library

Acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

The Cyclopedia Corporation of America has presented six volumes of the National Medical Monographs, as follows:

"Diseases of the Chest" by J. Arthur Myers (Fellow);
"The Management of Colitis" by J. Arnold Bargen (Fellow);
"Abnormal Arterial Tension" by Edward J. Stieglitz (Fellow);
"Commoner Diseases of the Skin" by S. William Becker;
"Obstetrics for the General Practitioner" by J. P. Greenhill;
"Industrial Medicine" by W. Irving Clark and Philip Drinker.

Eli Lilly and Company have presented to the Library of the American College of Physicians a bound volume entitled "Lilly Research Laboratories Dedication," in which are reproduced the addresses and proceedings of the dedicatory exercises held on October 11 and 12, 1934, in connection with the dedication of the new Lilly Research Laboratories.

Dr. Albert S. Hyman (Fellow), New York, N. Y., and Dr. Aaron E. Parsonnet (Fellow), Newark, N. J., have presented to the College Library their book entitled "The Failing Heart of Middle Life."

Dr. Oliver T. Osborne (Fellow), New Haven, Conn., has presented to the College Library his new book, "The Evaluation of Symptoms."

Other gifts not previously acknowledged are as follows:

Dr. Miles J. Breuer (Fellow), Lincoln, Nebr.—1 reprint;
Dr. Albert W. Bryan (Fellow), Madison, Wis.—3 reprints;
Dr. George T. Harding (Fellow), Columbus, Ohio—1 reprint;
Dr. Carl R. Howson (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Archibald L. Hoyne (Fellow), Chicago, Ill.—4 reprints;
Dr. Henry J. John (Fellow), Cleveland, Ohio—1 reprint;
Dr. Henry B. Mulholland (Fellow), University, Va.—7 reprints;
Dr. Alfred J. Scott, Jr. (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Clair L. Stealy (Fellow), San Diego, Calif.—2 reprints;
Dr. John M. Swan (Fellow), Rochester, N. Y.—5 reprints;
Dr. Henry H. Turner (Fellow), Oklahoma City, Okla.—4 reprints;
Dr. W. Bernard Yegge (Fellow), Denver, Colo.—5 reprints;

Dr. Arthur E. Lamb (Associate), Brooklyn, N. Y.—3 reprints;
Dr. Thomas D. Masters (Associate), Springfield, Ill.—2 reprints;
Dr. George W. Millett (Associate), Portland, Ore.—3 reprints;
Dr. W. G. Weston (Associate), Arkansas City, Kan.—2 reprints;
Dr. J. K. Williams Wood (Associate), Willow Grove, Pa.—1 reprint.

A testimonial dinner was tendered Dr. Ernest B. Bradley, President-Elect of the College, by the physicians of Fayette County, Kentucky, on June 27, in recognition of Dr. Bradley's being elected the President-Elect of the American College of Physicians.

Dr. Egerton L. Crispin (Fellow), Regent and Third Vice-President of the College, received the honorary degree of Doctor of Science on the occasion of the 106th Anniversary of his Alma Mater, Illinois College, at the Commencement Exercises on June 10.

Dr. Charles L. Brown (Fellow) has been appointed professor and head of the Department of Medicine in the Temple University School of Medicine, according to announcements by the University administration recently. Dr. Brown was at one time instructor in pathology, teaching fellow in medicine, and instructor in medicine in the Harvard University Medical School. He became assistant professor of internal medicine in the University of Michigan Medical School in 1928, and was advanced to associate professor of internal medicine in the same institution, beginning July 1929. He became a Fellow of the American College of Physicians in 1929.

Dr. William Gerry Morgan (Fellow), Secretary General of the College, resigned on July 1 as Dean of the Georgetown University School of Medicine. A farewell dinner in his honor was tendered him at the Mayflower Hotel, where sixty members of the Georgetown medical faculty were present to pay tribute to the services of their departing dean.

Dr. Morgan has retired to private practice, while continuing to serve as a Regent of Georgetown University.

Dr. Charles R. Reynolds (Fellow), Major General, U. S. Army, has succeeded Dr. Robert U. Patterson as the Surgeon General of the U. S. Army.

Dr. Herbert T. Kelly (Fellow), Philadelphia, Pa., was guest speaker on June 21 at the meeting of the Northampton County Medical Society at Easton, Pa., his subject

being "Dependable Laboratory Methods in the Diagnosis and Treatment of Diabetes Mellitus."

The following Fellows of the College were guest speakers on the program of the Tennessee Valley Medical Association and Post-Graduate Assembly at Knoxville, Tenn., June 26 to 27:

Dr. W. D. Stroud, Philadelphia, Pa.—"Coronary Disease, Including Angina Pectoris";

Dr. James E. Paullin, Atlanta, Ga.—"Arthritis";

Dr. Lyle Motley, Memphis, Tenn.—"Clinical Value of the Electrocardiogram in Diseases of the Heart."

Dr. Ralph H. Kuhns, Chicago, Ill., Instructor in Neuropsychiatry at the University of Illinois College of Medicine, will address the annual convention of the American Congress of Physical Therapy in Kansas City, September 9, on "Fever Therapy in Dementia Paralytica."

Dr. James W. Hunter, Jr. (Fellow), Norfolk, Va., became President of the Norfolk County Medical Society during June of this year. Dr. Walter B. Martin (Fellow), Norfolk, Va., was made President-Elect at the same time.

The Mississippi Valley Medical Society has been organized to conduct the Tri-State Post-Graduate Assembly of Illinois, Missouri and Iowa. The first annual meeting will be held in Quincy, Ill., on October 2, 3 and 4, 1935. Dr. Harold Swanberg (Fellow), Quincy, has been elected Secretary-Treasurer. Among Fellows who will address the first assembly are:

Dr. Albert Soiland, Los Angeles, Calif.;
Dr. William C. MacCarty, Rochester, Minn.

Dr. Albert S. Hyman (Fellow) will give two lectures upon resuscitation of the dying heart at the VII International Medical Post-Graduate Congress of the University of Brussels which meets at Spa, September 20 to October 2, 1935. Dr. Hyman will also speak before the Royal Academy of Medicine in Rome on October 5, and at the University of Bologna on October 7.

Dr. William B. Dewar (Fellow) and Dr. Hubert B. Haywood (Fellow), of Raleigh, N. C., have been appointed Professors of Medicine in the Wake Forest College School of Medicine.

Dr. Charles J. Bloom (Fellow), of New Orleans, has been elected President of the Louisiana Pediatric Society.

Dr. Louis H. Behrens (Fellow), of St. Louis, delivered the valedictory address to the graduates of the St. Louis College of Pharmacy on June 6. Dr. Behrens had graduated from this institution in 1888.

Local Meeting of the Fellows and Associates

of the

American College of Physicians in the District of Columbia

On April 16, 1935, a group of the civilian Fellows and Associates residing in the District of Columbia met at the Gallinger Municipal Hospital for a clinical session followed by luncheon. Dr. Thomas S. Lee, Professor of Cardiology at Georgetown University School of Medicine, gave a talk and clinical demonstration on the subject of auricular fibrillation. Dr. Walter A. Bloedorn, Professor of Medicine at George Washington University School of Medicine, gave a talk on the various types of obesity and their treatment. Dr. Charles P. Cake, Instructor in Clinical Medicine at Georgetown University School of Medicine, discussed the surgical treatment of pulmonary tuberculosis. Dr. Walter Freeman, Professor of Neurology at George Washington University School of Medicine, demonstrated on a patient with traumatic transection of the spinal cord the various technical procedures in diagnosis, including combined cisternal and spinal punctures. The session was presided over by Dr. Wallace M. Yater, Professor of Medicine at Georgetown University School of Medicine and Governor for the District of Columbia of the American College of Physicians. Dr. Wm. Gerry Morgan, Dean of the Georgetown University School of Medicine and Secretary-General of the American College of Physicians, addressed the group, reporting upon the various activities and the history of the College. Luncheon was tendered by Dr. Edgar A. Bocock, Superintendent of the hospital. This is the first of such meetings to be held in the District of Columbia. It is hoped that next year several adjoining states will arrange such a program together.

OBITUARIES

GEORGE E. BETHEL

Dr. George E. Bethel, Dean of the School of Medicine of the University of Texas, died April 17, 1935, from cardiac and renal complications of essential hypertension after an illness of about five months.

Although but 40 years of age, Dr. Bethel had rendered a signal service to the University of Texas in the field of medical education. After his graduation in medicine from the University of Texas in 1923 he became, successively, Adjunct Professor and Associate Professor in the Department of Anatomy in his alma mater, a service which extended over two years. During 1925 he was an intern in Philadelphia General Hospital, and in 1926 was advanced to the position of assistant chief resident physician of that institution. In 1927 and 1928 he was in charge of the Health Service of the University of Texas at the Main Branch of the University in Austin, from which position he was called to fill the deanship of the School of Medicine in Galveston in 1928. The latter office he held continuously up to the date of his death.

During his student years he won membership in the Alpha Omega Alpha honorary fraternity. He was a Fellow of the American Medical Association, and was elected to Fellowship in the American College of Physicians April 7, 1929.

Dr. Bethel's comparatively short term of office as Dean of the School of Medicine of the University of Texas, combined with the fact that he had not been in robust health for several years, prevented his attendance upon many gatherings of medical educators. Despite these handicaps, however, the excellence of his service in the deanship cannot be overstated. His one interest in life was the advancement of the Medical School; and the proper functioning and integration of its various units received his constant and thoughtful consideration. It is said that he knew personally and intimately every student in the School of Medicine. He knew those who were fitted for advanced study and research, as well as those who needed guidance, those who required assistance, and even those deserving punitive measures because of lagging scholarship or for other reasons. His constant and unfailing devotion to the welfare of the School of Medicine, its teaching staff and student body, was appreciated by all who knew him. He was widely known throughout the state, not only by the medical profession but among the laity and other professional and educational groups as well. So highly was he esteemed by the members of the Texas Legislature that the Senate of the state, which was in session at the time of his death, memorialized his passing with appropriate resolutions.

Dr. Bethel was a man of high moral principles, of abiding devotion to his duty and of unfailing fairness to all with whom he came in contact. His

capacity for inspiring students who came under his supervision with the loftiest ideals and the highest ethical principles will long be remembered.

CHARLES T. STONE, M.D., F.A.C.P.,
Governor for Texas

JOHN WILLIAM WARNICK

Dr. John William Warnick (Associate), Johnsonburg, Pennsylvania, died April 12, 1935, of diabetes mellitus and complications following an illness of more than a year. Dr. Warnick was born in 1863, and graduated from the University of Pittsburgh School of Medicine in 1896. He was a member of his county and state medical societies, and a Fellow of the American Medical Association. He was at one time county medical director, and for more than twenty years he was a member of the Board of Health in Johnsonburg. He was also President of the U. S. Board of Pension Examiners. He became an Associate of the American College of Physicians in 1925.